Defining Criteria For Rheumatoid Arthritis Patient-derived Disease Activity Score (PDAS) That Correspond To Disease Activity Score 28 (DAS28) And Clinical Disease Activity Index (CDAI) Based Disease States And Response Criteria

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Word count: up to 2000 words.
Abstract: up to 250 words.
Tables/illustrations: A maximum of 2 figures or tables.
References: up to 20
Key messages: Up to 3 (maximum 15 words each).

Abstract

Objective

Two versions of a patient-based disease activity score (PDAS) 1 and 2 (with and without ESR) have been developed and validated in rheumatoid arthritis (RA). The objective of this study is to define PDAS1 and PDAS2 based criteria for remission, low, moderate and high disease activity and responses to treatment.

Method

Using receiver operator characteristic (ROC) curves, the optimal thresholds for PDAS1 and PDAS2 that correspond to validated assessor-based Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI) disease statuses were determined. Data from RA patients initiated on disease modifying drugs were used to determine optimal thresholds for PDAS1 and PDAS2 that corresponded to EULAR good and moderate responses. Agreement with DAS28, CDAI and EULAR response criteria were assessed by Cohen's kappa (κ) statistics.

Results

Threshold for PDAS1 and PDAS2 demonstrated fair to moderate agreement with DAS28 (κ = 0.44 [95% confidence interval: 0.40-0.50] and 0.31 [95% CI: 0.25-0.38]) and CDAI (κ = 0.27 [95% CI: 0.22-0.33] and 0.42 [95% CI: 0.35-0.49]) disease statuses respectively, which were similar to agreement between DAS28 and CDAI (κ = 0.54 [95% CI: 0.46-0.61]) within this group. Agreement between EULAR good and moderate response with PDAS1 and PDAS2 were κ = 0.46 (95% CI: 0.27-0.64) and 0.38 (95% CI: 0.20-0.56), respectively.

Conclusion

Thresholds for disease activity statuses and response to treatment for PDAS1 and PDAS2 have been established. They have comparable agreement to assessor-based criteria.

(Abstract word count: 232)

Key Messages

1. We established thresholds for disease activities and response criteria for Patient-based Disease Activity Scores.
2. They have moderate agreement with Disease Activity Score 28 and Clinical Disease Activity Index.
3. They would be useful for rheumatoid arthritis patients self-monitoring to facilitate treat-to-target strategy.

Introduction

Rheumatoid Arthritis (RA) affects 0.5-1% of the population [1]. Inflammation leads to joint damage resulting in pain, swelling and disability [2]. Sustained suppression of the inflammation has been shown to be important in preventing joint damage in RA [3]. Therefore, treat-to-target towards remission or low disease activity is the current standard of care recommended by National Institute for Health and Clinical Excellence [4], European League Against Rheumatism [5] and American College of Rheumatology [6]. Monitoring disease activity regularly is important in achieving this goal. Current recommendation is to assess patients 1-3 monthly using measures such as Disease Activity Score28 (DAS28)[7], Simplified Disease Activity Index (SDAI)[8] or Clinical Disease Activity Index (CDAI)[9] all of which require patients attending hospital to be assessed by a healthcare professional. Patients with RA should self-monitor disease activity at home, akin to diabetic patients self-monitoring blood sugar so that they can seek medical advice promptly when disease is active.

Patient Disease Activity Score (PDAS) is a validated patient self-assessed score of disease activity [10], which does not require any prior training. The preliminary items of the PDAS were selected based on a systematic review of disease activity self-assessment items. It included all the patient-reported outcome domains from the Outcome Measure in Rheumatology (OMERACT) core data set i.e. pain, patient global (PGA), Health Assessment Questionnaire (HAQ). It also added early morning stiffness (EMS), fatigue, patient self-assessed tender count (TJC) and patient self assessed swollen joint count (SJC)[11]. Two versions of the PDAS were developed and validated: PDAS with the ESR (PDAS1= 0.019 x (PGA out of 100) + 0.842 x ln(ESR + 2) + 0.432 x ln(patient 50 TJC + 2) + 0.271 x (HAQ) or without ESR (PDAS2
= 2.667 + 0.021 x (PGA out of 100) + 0.483 x (HAQ) + 0.033 x (patient 28 SJC) + 0.002 x (EMS in minutes)).
Components of PDAS1 and 2 were selected based on best statistical modelling against gold standard at the time, Disease Activity Score (DAS28), therefore correlate highly with DAS28 but different components were selected for PDAS1 and 2. Laboratory tests were removed from PDAS2 intentionally, so as to develop an instrument that assess disease activity without the need for a blood test. Internal consistency, test-retest reliability, criterion and construct validity were demonstrated during validation. Moreover, the sensitivity of change of PDAS1 and PDAS2 is also similar to DAS28. Interestingly, for patients with RA and concomitant fibromyalgia, tender joint count and pain score are often higher than patients without fibromyalgia[12]. However, swollen joint count including patient self-assessed swollen joint count is not affected. Consequently for PDAS2, the scoring is more weighted on self-assessed swollen joint count than tender joint count, which differs from DAS28.

Like DAS28, PDAS1 and PDAS2 are continuous status measures. However, thresholds for defining response to treatment and remission have not yet been established. The objective of this study is to define thresholds, based on PDAS1 and PDAS2, for disease status: remission, low, moderate and high disease

activities and European League Against Rheumatism (EULAR) good and moderate responses[13] to treatment.

Method

Data from 299 RA patients, originally used to develop and validate PDAS[10] were used for this study. Briefly, they were patients who attended Rheumatology outpatients clinics who met the 1987 American College of Rheumatology criteria for RA[14]. In addition, data from 56 patients who had started disease-modifying anti-rheumatic drugs (DMARDs) (50 patients) or biologic agents (6 patients) and were seen 6 months apart were used to determine optimal thresholds for PDAS1 and PDAS2 corresponding to EULAR responses criteria. Conventional disease outcome assessments were also performed, including tender and swollen joint counts (28 joints), and were used to calculate the DAS28 and Clinical Disease Activity Index (CDAI).

The study was approved by the South Thames Multicentre Research Ethics Committee and all patients gave written informed consent.

Determining the optimal thresholds

Receiver operator characteristic (ROC) curves were plotted to determine the optimal thresholds for PDAS1 and PDAS2 that corresponded to validated DAS28 and CDAI criteria for remission, mild, moderate and high disease activity states. Optimal thresholds were obtained by maximising the average of sensitivity and specificity. Agreement with DAS28 and CDAI thresholds and EULAR response criteria were assessed with Cohen's kappa (κ) statistics. Intraclass correlation coefficient (ICC) was used to assess agreement between PDAS1 and PDAS2 with DAS28 and CDAI as continuous variables. Kappa value ranging from 0.21 to 0.40 is conventionally taken as fair agreement, 0.41 to 0.60 moderate, and 0.61-0.80 substantial[15]. The number of patients scoring extreme discordance was also calculated, i.e. scoring remission in one index and high activity in another, or good response in one and non-response in another.

Results

Patients

299 RA patients with established RA were included in this analysis. 225 (75%) were female and 74 (25%) were male. Mean age was 60 years (standard deviation 13 years) with average disease duration of 9 years (SD 11 years). Most of the patients 81% were rheumatoid factor positive. The mean age of the 56 patients who were started on a new treatment, was 55 years (SD 14 years). The mean disease duration was 8 years (SD 10 years). Eighty-eight percent of the patients were female and 63% were rheumatoid factor positive.

Thresholds for remission, low, moderate and high disease activity for PDAS1 and PDAS2

The corresponding thresholds for differentiating DAS28 remission, low, moderate and high disease activity states for PDAS1 were 3.5, 4.5 and 4.8; and 3.8, 4.6 and 5.0 for PDAS2 respectively. Scatter plots of PDAS1&2 to DAS28 and CDAI are in Figure 1 and Figure 2 respectively. Areas under curve (AUC) for all the above ROC curves were from 0.89 to 0.95 (all $p<0.001$). Sensitivities for PDAS1&2 to DAS28 were respectively: remission versus not in remission (92%, 90%), remission and low versus moderate and high disease activity (99%, 89%), remission, low or moderate activity versus high activity (95%, 79%). Correspondingly, specificities for PDAS1&2 to DAS28 for these states were respectively: 89%, 71%; 61%, 69%; 74%, 82%.

Similarly for CDAI, AUC for all ROC curves were from 0.86 to 0.93 (all $p<0.001$). Sensitivities for PDAS1&2 to CDAI were respectively: remission versus not in remission (70%, 84%), remission or low disease activity versus moderate or high disease activity (77%, 88%), remission, low or moderate activity versus high activity (88%, 79%). Correspondingly, specificities for PDAS1&2 in these states were respectively: 91%, 95%; 85%, 80%; 69%, 91%.

These thresholds demonstrated fair to moderate agreement with DAS28 disease activity categories was observed: $\kappa = 0.44$ (95% CI: 0.40-0.50) for PDAS1 and 0.31 (95% CI: 0.25-0.38) for PDAS2. ICC between DAS28 and PDAS1 was 0.78 (95% CI: 0.72-0.82) and PDAS2 was 0.65 (95% CI: 0.57-0.71). Corresponding agreements with CDAI were $\kappa = 0.27$ (95% CI: 0.22-0.33) for PDAS1 and 0.42 (95% CI: 0.35-0.49) for PDAS2. ICC between CDAI and PDAS1 was 0.65 (95% CI: 0.58-0.71) and PDAS2 0.68 (95% CI: 0.62-0.74). These agreements were similar to those of CDAI and DAS28 within the same group of patients, with $\kappa = 0.54$ (95% CI: 0.46-0.61) and ICC 0.81 (95% CI: 0.77-0.85). Extreme discordance with DAS28 was uncommon: none in PDAS1 and only two patients (0.7%) in PDAS2. Extreme discordance with CDAI was also uncommon: nine patients (3%) in PDAS1, and one patient (0.3%) in PDAS2. There was no extreme discordance between DAS28 and CDAI.

Definitions for Good, Moderate and Non-response

PDAS1 and PDAS2 based definitions for good, moderate and non-response are summarised in Table 1. Any patient with a reduction of less than 0.4 or 0.3 of PDAS1 and PDAS2 respectively were non-responders. A good responder was defined by a reduction in PDAS1 score by at least 0.8 and an end PDAS1 score of

≤4.5. For PDAS2, the corresponding values were a reduction of >1.2 and an end PDAS2 score of ≤4.6. They aligned well with EULAR response criteria with AUC under ROC ranged from 0.88 to 0.93 (all $p<0.001$). Sensitivities for PDAS1&2 to DAS28 responses were respectively: non-response versus moderate or good response (75%, 72%), and no or moderate response versus good response (100%, 68%). Corresponding specificities for PDAS1&2 were respectively: 94%, 89%; 77%, 93%.

Agreement of EULAR response criteria and PDAS1&2 were moderate: $\kappa = 0.46$ (95% CI: 0.27-0.64) and 0.38 (95% CI: 0.20-0.56) respectively, and ICC = 0.71 (95% CI: 0.56-0.82) and 0.49 (95% CI: 0.26-0.67) respectively. The agreement of DAS28 and CDAI within this patient group was also moderate ($\kappa = 0.55$, 95% CI 0.36-0.73). Extreme discordance with DAS28 response was uncommon: one patient (2%) in PDAS1 and four patients (7%) in PDAS2. On the other hand, extreme discordance with CDAI was less uncommon: eight patients (14%) in PDAS1 and four patients (7%) in PDAS2. Notwithstanding, extreme discordance between DAS28 and CDAI responses occurred in 3 patients (5%).

Discussion

In RA, there are many validated tools to assess disease activity, which are extensively used in clinical trials and routine daily practice. They are fundamental to delivering the current standard of care: treat-to-target. All these tools required an assessor conducting an examination to determine the number of tender and swollen joints. Therefore, patients need to attend clinics for these assessments to be conducted. Many patients complain of disease flare in between clinic visits. The PDAS1&2 scores were developed to enable patients to self-assess disease activity. They have been validated and shown to correlate well with DAS28 and CDAI, are sensitive to change [10].

Here we use standard statistical modelling to define thresholds for defining high, moderate, low disease activity and remission as well as good, moderate and non-response for PDAS1 and PDAS2. They have comparable agreement to current gold standard assessor based criteria, DAS28 and CDAI. Indeed, the degree of agreement was comparable to that of DAS28 and CDAI within this patient group ($\kappa = 0.55$, 95% CI: 0.36-0.73), which was similar to that in CORRONA study ($\kappa = 0.57$)[16] and in original CDAI derivation study ($\kappa = 0.52$)[17]. Although PDAS2 appeared to have comparatively lesser agreement with DAS28 than PDAS1 ($p<0.05$, non-overlapping 95% CI) by kappa statistics and ICC, this not surprising ESR was a component of DAS28 and PDAS1. Indeed, PDAS2 did have better agreement with CDAI than PDAS1 by kappa statistics, but not ICC. PDAS2 (without ESR) has the clinical advantage of obviating the need for blood test.

Gross mis-classification of disease activities or response criteria was uncommon, as evident by the low proportion of extreme discordance (0-3% for activities and 2-14% for response), given that even 5% of patients would have extreme discordance between DAS28 and CDAI responses. The moderate disease activity interval for PDAS is relatively short, and many patients classified as moderate disease by DAS28 are in high disease activity by PDAS. However, in terms of treat-to-target strategy, the difference is insignificant, as these patients should be treated to achieve remission or low disease activity status. The major difference in DAS28 and PDAS is in the assessment of joint count. First, patients score higher on tender joint count than assessor [20,21]. Second, interobserver variability in assessor-based tender joint and swollen joint count is very high with coefficient of variation of up to 204% [22]. The narrow range of PDAS is likely to result from reduced interobserver variability. In clinical trials, protocols often stipulate joint count assessment be performed by one assessor. In clinical practice, this is not feasible, joint counts are often carried out by different assessors.

The development of PDAS is not intended to replace assessor based disease activity tools, rather the aim is to develop a complimentary tool that facilitates treat-to-target by allowing patients to monitor disease at home. PDAS1 and 2 are being used in the Canadian Early Arthritis Cohort study and the UK Health Technology Assessment funded Reducing Arthritis Fatigue Trial.

Defining self-assessed disease activity states may be useful to prompt patients to seek medical advice when RA is active. However, further studies will be needed to test the clinical effectiveness of PDAS in implementing treat-to-target strategy.

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Table 1: Definitions of good, moderate and non-response based on Patient based Disease Activity Score (PDAS) 1 and 2.

***PDAS1 response criteria*:**	**Improvement**		
Final score	>0.8	0.4 - 0.8	≤0.4
PDAS1≤4.5	**Good**	**Moderate**	**No**
4.5 < PDAS1≤ 4.8	**Moderate**	**Moderate**	**No**
PDAS1 > 4.8	**Moderate**	**No**	**No**
PDAS2 response criteria:	**Improvement**		
Final score	>1.2	0.3 - 1.2	≤0.3
PDAS2≤4.6	**Good**	**Moderate**	**No**
4.6 < PDAS1≤ 5.0	**Moderate**	**Moderate**	**No**
PDAS1 > 5.0	**Moderate**	**No**	**No**

Legends for Figures:

Figure 1: (a) Scatter plots of PDAS1 to DAS28. Circles are patients in PDAS1 remission. Triangles are patients in PDAS1 low disease activity. Squares are patients in PDAS1 moderate disease activity. Pentagons are patients in PDAS1 high disease activity. (b) Scatter plots of PDAS2 to DAS28. Circles are patients in PDAS2 remission. Triangles are patients in PDAS2 low disease activity. Squares are patients in PDAS2 moderate disease activity. Pentagons are patients in PDAS2 high disease activity.

Figure 2: (a) Scatter plots of PDAS1 to CDAI. Circles are patients in PDAS1 remission. Triangles are patients in PDAS1 low disease activity. Squares are patients in PDAS1 moderate disease activity. Pentagons are patients in PDAS1 high disease activity. (b) Scatter plots of PDAS2 to CDAI. Circles are patients in PDAS2 remission. Triangles are patients in PDAS2 low disease activity. Squares are patients in PDAS2 moderate disease activity. Pentagons are patients in PDAS2 high disease activity.

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