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Cumulative Patient-based Disease Activity Monitoring in Rheumatoid Arthritis – Predicts Sustained remission, Flare and Treatment Escalation

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Abstract:	Objective. Patient-based Disease Activity Score 2 (PDAS2) had been developed for RA patients to self-assess and record disease activity in between clinic visits. This study explored the clinical utility of time-integrated cumulative PDAS2 (cPDAS2) on predicting sustained remission or low disease activity state (LDAS), flare and treatment escalation. Methods. We recruited 100 patients to record PDAS2 at home fortnightly between two consecutive clinic visits. Rheumatologists adjusted treatment according to disease activity recorded during clinic consultation while blinded to home PDAS2 scores. cPDAS2 calculated from the area-under-curve of all PDAS2 scores were compared with disease activities at both visits. cPDAS2 and ΔcPDAS2 (change from PDAS2 at the first visit) were tested to determine their ability to predict ACR/EULAR remission, SDAI flare-up (from remission/LDAS to moderate/high disease activity) and treatment escalation. Optimal cut-points were determined by Receiver Operator Characteristic curve. Results. Mean age was 59 years, mean RA duration 14 years, 90% female, 71% seropositive and 64% in remission/LDAS. The home PDAS2 completion rate was 92%. PDAS2 scores were done 7.5 times every 15 days over a 16-week follow-up (all medians). The sensitivity of cPDAS2 in predicting Boolean/SDAI remission at two visits, DAS28, SDAI and CDAI remission or LDAS were 93%, 84%, 73% and 80% respectively. cPDAS2≥0.29 predicted flare (P=0.04), with specificity 79% and negative predicting value (NPV) 88%. Rheumatologists' decision to escalate treatment was predicted by (cPDAS2≥4.33 and ΔcPDAS2≥0.059) (P=0.007) with specificity 88% and NPV 89%, and (cPDAS2≥4.33 or ΔcPDAS2≥0.059) (P=0.02) with both sensitivity and NPV 100%. Conclusion. PDAS2 monitoring at home is feasible. cPDAS2 is useful to predict flare and treatment escalation.
Suggested Reviewers:	Vivian P Bykerk bykerkv@hss.edu Expert in patient reported outcome in rheumatoid arthritis and had published extensively on this topic
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	Peter Cheung peter_cheung@nuhs.edu.sg Dr. Peter Cheung had a number of publication on patient-physician discordance in a range of rheumatic conditions
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Running title: **Cumulative PDAS2**

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Cumulative Patient-based Disease Activity Monitoring in Rheumatoid Arthritis – Predicts Sustained remission, Flare and Treatment Escalation

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Abstract

Objective. Patient-based Disease Activity Score 2 (PDAS2) had been developed for RA patients to self-assess and record disease activity in between clinic visits. This study explored the clinical utility of time-integrated cumulative PDAS2 (cPDAS2) on predicting sustained remission or low disease activity state (LDAS), flare and treatment escalation.

Methods. We recruited 100 patients to record PDAS2 at home fortnightly between two consecutive clinic visits. Rheumatologists adjusted treatment according to disease activity recorded during clinic consultation while blinded to home PDAS2 scores. cPDAS2 calculated from the area-under-curve of all PDAS2 scores were compared with disease activities at both visits. cPDAS2 and ΔcPDAS2 (change from PDAS2 at the first visit) were tested to determine their ability to predict ACR/EULAR remission, SDAI flare-up (from remission/LDAS to moderate/high disease activity) and treatment escalation. Optimal cut-points were determined by Receiver Operator Characteristic curve.

Results. Mean age of the patients was 59 years, mean RA duration 14 years, 90% were female, 71% seropositive and 64% in remission/LDAS. The home PDAS2 completion rate was 92%. PDAS2 scores were done 7.5 times every 15 days over a 16-week follow-up (all medians). The sensitivity of cPDAS2 in predicting Boolean/SDAI remission at two visits, DAS28, SDAI and CDAI remission or LDAS were 93%, 84%, 73% and 80% respectively. cPDAS2≥0.29 predicted flare (P=0.04), with specificity 79% and

negative predicting value (NPV) 88%. Rheumatologists' decision to escalate treatment was predicted by (cPDAS2≥4.33 and ΔcPDAS2≥0.059) (P=0.007) with specificity 88% and NPV 89%, and (cPDAS2≥4.33 or ΔcPDAS2≥0.059) (P=0.02) with both sensitivity and NPV 100%.

Conclusion. PDAS2 monitoring at home is feasible. cPDAS2 is useful to predict flare and treatment escalation.

(Abstract word count: 266)

Key words:

Rheumatoid arthritis; Outcome measures; Behaviour; DMARD

Statement of Significance

What was known before the study:

Patient-based Disease Activity Scores 2 (PDAS2), without evaluator joint assessment or laboratory result, has previously been validated and shown to correlate with Disease Activity Score (DAS28) in patients with rheumatoid arthritis at the clinic

What was learnt from this study:

1. It is feasible for patients to self-assess PDAS2 between clinic visits

2. Time-integrated cumulative score (area-under-curve) is useful to inform sustained remission or low disease activity or flare

3. It may be used to inform rheumatologists to escalate disease modifying drug.

INTRODUCTION

Treat-to-target is the current standard of care in rheumatoid arthritis (RA) (1, 2). Remission should be the treatment target though low disease activity is acceptable especially in patients with long-standing disease with multiple disease modifying anti-rheumatic drug (DMARD) failures and co-morbidities that pose contraindication to DMARDs. Such recommendation is underpinned by evidence showing that time-integrated disease activity correlates with radiographic joint damage (3). Sustained remission is important if joint damage is to be aborted (4). However, disease flares are common in RA. In a cohort of stable RA patients, 16-32% experienced a disease flare in between two clinical visits three to six months apart (5). Disease flares in patients who have been in remission are not only associated with radiographic joint damage (4) but also increased risk of cardiovascular events (6). In these ways, cumulative disease activity is an important prognostic indicator in RA. Regular assessment of disease activity to attain low disease activity state (LDAS) or remission by tailoring the regime and dosage of DMARDs is an integral part of the treat-to-target strategy. The European League Against Rheumatism (EULAR) 2019 update recommended monitoring should be frequent in active disease (every 1–3 months) (2). Commonly used disease activity measurements such as Disease Activity Score 28 (DAS28) (7), Simplified Disease Activity Index (SDAI) (8) and Clinical Disease Activity Index (CDAI) (9) are assessor-based, with the former two necessitate concomitant blood testing for acute phase reactants. Moreover, often due to the constraints in routine clinical practice, frequent monitoring as stipulated by EULAR recommendations may be less feasible in the context of active disease (active 1-3 months), while monitoring less

frequently in the context of less active disease would seem to be feasible in many settings.

Patient-based Disease Activity Score 2 (PDAS2) has been developed to allow RA patients to self-assess disease activity without requiring any laboratory blood tests (10), and also to overcome the inter-observer variability of tender and swollen joint counts that can be up to two-fold (11). PDAS2 is a composite score comprising of four components: Patient Global Assessment (PGA) which is patient's perception of RA activity on a 100 mm range visual analogue scale (12); Health Assessment Questionnaire (HAQ) score (13), having a range of 0–3 points, records the self-rated functional ability in managing activities of daily living; patient 28 swollen joint count (SJC) is a self-rated count of presence/absence of joint swelling in the same 28 joints as DAS28 (7); and early morning stiffness (EMS) duration is the maximal duration of joint stiffness in the morning up to five hours. From regression analysis, PDAS2 is given by:

$$\mathbf{PDAS2} = 2.667 + 0.021 \times (\mathbf{PGA}\ \text{out of}\ 100) + 0.483 \times \mathbf{HAQ} + 0.033 \times (\mathbf{patient\ 28\ SJC}) + 0.002 \times (\mathbf{EMS}\ \text{in minutes})$$

PDAS2 has been validated and shown to correlate with assessor-based DAS28 and CDAI (10). From the developmental regression analysis model, the four components in PDAS2 (PGA, HAQ, patient 28 SJC and EMS) explained 55% of the variation in DAS28. In particular, PGA accounted for 44% of the variance, whereas HAQ, patient 28 SJC and EMS a further 5%, 4% and 1% respectively.

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Furthermore, the corresponding disease activity statuses cut-points and response criteria have been published (14). PDAS2 scores < 3.8, 3.8–4.6, >4.6–5.0, > 5.0 correspond to remission, low, moderate and high disease activities respectively. Although the feasibility of using PDAS2 to assess disease activity between clinic visits had not been formally assessed before the current study, intuitively a time-integrated i.e. cumulative PDAS2 (cPDAS2) should be capable of recording overall disease activity over time. PDAS2 does not intend to replace assessor-based disease activity indices, which are crucial to patient assessment, in guiding DMARD titration according to the treat-to-target principle. Indeed, home monitoring of RA disease activity by PDAS2 can reveal the course of RA activities and possibly to notify the patient and healthcare providers of a potential flare that should be acted on timely with DMARD adjustment. As in many chronic diseases, targeting overall disease activity, rather than spot measurement, results in better long-term patient outcomes. For example, in managing diabetes mellitus, targeting HbA1c results in better outcomes such as reduced microvascular complications than targeting fasting or spot glucose levels (15) and hypertension-associated end-organ damage is more closely related to ambulatory blood pressure than clinic blood pressure measurements (16).

This study aims to explore whether home PDAS2 monitoring of RA activity between clinic visits is feasible, how the time-integrated summative home PDAS2 scores and patterns correlate with different disease activity statuses and their changes (especially flare) between clinic visits, and if they are able to correlate with rheumatologists' intention to escalate DMARD.

SUBJECTS AND METHODS

A cohort of 100 consecutive RA patients was recruited from a specialist rheumatology clinic in Hong Kong. Patients were eligible if they met either the 1987 American College of Rheumatology (ACR) (17) or 2010 EULAR/ACR criteria for RA (18) and willing to provide signed informed consent. The study was approved by the Hong Kong Hospital Authority Kowloon Central Cluster Ethics Committee (KC/KE-15-0141/ER-1).

Sample Size Calculation. There are four components in PDAS2. A rough guide suggested by Green (19) is that the number of subjects for correlation study is 50+6× (number of independent variables). Therefore 74 subjects would be sufficient. On the other hand, another local cross-sectional PDAS validation study of 100 RA patients showed that 48% were in remission or low disease activity and 52% in moderate or high disease activity (20). Assuming an upper limit of half of the patients in remission or low disease activity would flare up to moderate or high disease activity and those in moderate or high disease activity would remain so in the following clinic visit, there would also be approximately total 76 (=48/2+52) patients who might be considered for escalating DMARD treatment. Then the inclusion of the whole 100 RA patients in the local cohort would appear to be sufficient by this crude estimation.

Disease Assessment. Rheumatologists in the Specialist Clinics recorded the assessor-based tender and swollen joints count (28 joints) and physician global assessment (0–100 mm) as per standard clinical practice. Blood tests were checked one week before every clinic visit: Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) were included.

Questionnaires. Patients were given a self-assessment questionnaire for PDAS2 while waiting for consultation in every clinic visit. In addition, they completed the same PDAS2 questionnaire at home fortnightly in between two consecutive rheumatology clinics or more often if needed. Patients would return the set of completed questionnaires when they attended the second clinic. Rate of missing data in total completed questionnaires and in individual patients was recorded, and data were imputed using last observation carried forward method.

DMARD Adjustment. Rheumatologists added or withdrew adjusted disease modifying anti-rheumatic drugs (DMARD) or stepped up or down their dosages according to RA disease activity following EULAR recommendations (21) while blinded to PDAS2 scores recorded at home. Adjustment due to side-effects or non-compliance were noted but not counted as the rheumatologists' intention to adjust DMARD according to RA activity.

Mathematical Treatment of Raw Data and Statistical Analysis. (Table 1) The cumulative PDAS2 score (cPDAS2), which reflects the totality of disease activity as assessed by PDAS2, was calculated by the area-under-curve method using all interval PDAS2 scores between the first and second visits (Figure 1):

$$\text{cPDAS2} = [\sum (\text{PDAS2 score} \times \text{time interval between scores})] / \text{follow-up duration}$$

And the change of cPDAS2 score (ΔcPDAS2) is given by:

$$\Delta\text{cPDAS2} = \text{cPDAS2} - \text{PDAS2 at the first visit}$$

Standard deviation (SD) of a patient's PDAS2 scores would reflect the fluctuation of RA activities between two clinic visits, an aspect not revealed by the scores at the two visits (Figure 2). Furthermore, "cPDAS2 above two-visit PDAS2 mean" could reflect the recency of a flare (Figure 3a and 3b) as the "two-visit PDAS2

mean" was at the mid-point of a theoretically uniform rise of RA activity and the direction of the difference with cPDAS2 (area-under-curve), i.e. positive or negative, would respectively signify a longstanding or a recent flare.

The disease activity statuses of cPDAS2 score were compared with disease activity at the second visit using conventional composite indices: DAS28, SDAI and CDAI and ACR/EULAR remission criteria (22) (Boolean and SDAI) by cross-tabulation. Specificity, sensitivity, positive and negative likelihood ratios (LR), positive predictive value (PPV) and negative predictive value (NPV) were calculated. Both cPDAS2 and ΔcPDAS2 scores of those patients having more active disease as defined by SDAI score shifting from remission/low to moderate/high disease activity) was compared to those patients whose disease activity did not change using unpaired non-parametric Mann-Whitney U test. SDAI was chosen as it aligns with ACR/EULAR remission criteria. Similarly, cPDAS2 and ΔcPDAS2 scores, alongside with SDAI and change of SDAI scores, will be compared between those patients whose attending rheumatologists decided to escalate DMARD and those who had their DMARD regime continued or reduced. Receiver Operator Characteristic (ROC) curve was constructed to determine the cut-points with optimal sensitivity and specificity and largest area-under-curve (AUC), for cPDAS2 and ΔcPDAS2 to predict SDAI remission/low disease activity (LDAS), flare and rheumatologists' decision to escalate DMARD.

Statistical significance of type I error α was set to be $P<0.05$, two-sided and not adjusted for multiple comparisons. IBM SPSS Statistics 23.0 software (Chicago, IL, US) was used.

RESULTS

From the 100 patients in the cohort, 92 patients (92%) returned written questionnaires at the second clinic visit which took place at a median interval of 16 weeks (range 27–483 days, interquartile range IQR 83 days). The median number of home questionnaires done by an individual patient was 7.5 (range 1–16, IQR 6) and the median interval of questionnaires done by an individual patient was 15.3 days (range 7–131 days, IQR 4.4 days). The clinical characteristics of those who completed home PDAS2 questionnaires were similar to those who did not (Table 2) except that physician global assessment was higher in non-completers compared to completers (median 45 versus 28 out of 100, P=0.01) while there was no statistical significant difference in other composite disease activity scores.

Further analysis was limited to these 92 patients who had home PDAS2 data. Missing data occurred in 13 (14%) patients in which six entries (0.6% of total 967 questionnaire completions) in two patients were on morning stiffness duration and 73 (7.5%) entries in 11 patients were on patient global assessments. Patients' mean age was 59 years (SD 12 years) and mean RA disease duration 14 years (SD 9 years) (Table 2). Most of them were female (83 patients, 90%), seropositive for rheumatoid factor (65, 71%) and in remission/LDAS at the first visit (59, 64%). DMARDs and biologics treatments included methotrexate (58 patients, 63%), hydroxychloroquine (30, 33%), sulphasalazine (24, 26%), prednisolone (13, 14%), leflunomide (6, 7%), tocilizumab (17, 19%) and tumour necrosis factor antagonists (9, 10%).

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Between the first and second clinic visits, 48 (52%) patients remained in SDAI remission/LDAS and 23 (25%) stayed in moderate/high activities, while 11 (12%) had a flare and 10 (11%) improved (from moderate/high activities to remission/LDAS).

Sustained Remission. For the 14 (15%) patients in ACR/EULAR remission (Boolean and SDAI remission) at both visits, 13 were in cPDAS2 remission, and one in LDAS with a cPDAS2 value of 3.82, just above the cut-point 3.8. Sensitivity was 93%, specificity 63%, LR- 0.1 and NPV 98% (Table 3). Median of home PDAS2 scores SD in those who were in ACR/EULAR remission at both visits was 0.068, compared to those who had only remission at one visit (0.174) and those who were never in remission (0.171) (P=0.02).

There were 37 (40%), 48 (52%) and 45 (49%) patients in DAS28, SDAI and CDAI remission/LDAS respectively (Table 3). The optimal cut-point for cPDAS2 corresponding to SDAI remission/LDAS was 4.10 (AUC=0.85 [95% CI: 0.76, 0.93], P<0.001) and home PDAS2 scores SD was 0.146 (AUC=0.71 [95% CI: 0.62, 0.82], P=0.001). Combination of these two criteria yielded a specificity of 91% and LR+ 6.0 (“and”); sensitivity of 92% and LR- 0.2 (“or”) (Table 4).

Arthritis flare. Of the 59 patients who were in SDAI remission/LDAS at the first visit, 11 (19%) had a flare at the second visit, with their SDAI score increased by 6.90 compared to 0.12 in those who did not flare (P<0.001). The median clinic PDAS2 score also rose by 0.52 in those who flared, while those who did not flare had their median PDAS2 score unchanged (P<0.001). Median cPDAS2 score was 3.70 in those who flared compared to 3.37 in those who did not, which was not statistically significant (P=0.07).

On the other hand, the median ΔcPDAS2 score in those who flared was 0.30 compared to 0.05 in those who did not (P=0.04). Furthermore, ROC curve AUC was 0.71 (95% CI: 0.57, 0.84) (P=0.04), with optimal cut-point at ΔcPDAS2 score 0.29 to predict flare (Figure 4a). Sensitivity was 55%, specificity 79% and NPV 88%.

DMARD escalation. At the second visit, rheumatologists decided to escalate DMARD treatment in 16 (17%) patients, and proportionally more in patients with higher RA disease activities (Table 5) with the following DMARD escalation: increasing dose of methotrexate (five) and sulphasalazine (one), adding methotrexate (one), leflunomide (three), abatacept (one), intramuscular steroid injection (four) and oral steroid (one). Of these 16 patients, seven had SDAI flare and seven had persistent moderate or high activity. Three (19%) patients eventually refused DMARD escalation and there was no statistical significance difference in cPDAS2, ΔcPDAS2, SDAI, PGA, physician global assessment, age and gender distribution between them and those who followed rheumatologists' decision to escalate DMARD. Median SDAI score was 16.55 (IQR 9.4) in those who had DMARD increased, compared to 6.00 (IQR 8.3) in those who had DMARD unchanged or reduced (P<0.001). The median SDAI score changes between two visits were an increment of 2.70 and a decrement of 0.10 respectively in these two groups (P<0.001). Specifically, seven (44%) patients had SDAI flare, seven (44%) in persistent high activity, one (6%) persistent LDAS and one (6%) transiting from moderate activity to LDAS. Also, at the second visit, median PDAS2 score at the second visit increased by 0.28 and 0.00 respectively in these two groups (P=0.04). Notably, the median cPDAS2 score for those who had DMARD escalated was

4.46 compared to 3.77 in those who had DMARD regime continued or stepped down (P=0.03), while the corresponding ΔcPDAS2 score was 0.18 and 0.05 (P=0.05).

ROC curve AUC for cPDAS2 was 0.72 (95% CI:0.57, 0.86) (P=0.007) with optimal cut-point at 4.33 to predict decision of DMARD escalation, though the sensitivity was only 63% and specificity 75%. ROC curve AUC for ΔcPDAS2 was 0.68 (95% CI: 0.56, 0.80) (P=0.02), with optimal cut-point at 0.059, and sensitivity being 81% and specificity 53%. Combining these two criteria (cPDAS2 score and/or ΔcPDAS2) improved sensitivity and specificity. For cPDAS2 score ≥ 4.33 and ΔcPDAS2 ≥ 0.059, ROC curve AUC was 0.72 (P=0.007) (95% CI: 0.57, 0.86) (Figure 4b) and specificity could be improved to 88% and NPV 89%. For cPDAS2 score ≥ 4.33 or ΔcPDAS2 ≥ 0.059, ROC curve AUC was 0.69, (P=0.02) (95% CI: 0.56, 0.80) (Figure 4c) and both sensitivity and NPV reached 100% (Table 6). In further details, cPDAS2 was more predictive of rheumatologists' decision to escalate DMARD in the subgroup of patients who had persistent moderate or high RA activity (P=0.009); and in contrast, ΔcPDAS2 was more predictive in the subgroup of patients who had an arthritis flare (P=0.024) (Table 7).

A trend appeared that oral or intramuscular steroid was more often chosen (four out of seven patients, 57%) for those with negative values of cPDAS2 above two-visit PDAS2 mean ("recent flare", ranging from –0.011 to –0.513) compared to only one out of eight patients (13%) with positive values of cPDAS2 above two-visit PDAS2 mean ("longstanding flare", ranging from 0.017 to 0.758) was considered intramuscular steroid (P=0.12, Fisher's exact test) (Figure 5).

CUMULATIVE PDAS2

Sensitivity analyses using methods of exclusion of patients and imputation with extreme values demonstrated the robustness of the above findings on SDAI flare and rheumatologists' intention to escalate DMARD at the second visit at a group level (Supplemental material Table 1).

DISCUSSION

This study uniquely used time integrated/cumulative (AUC) concept to explore the utility of a patient-reported outcome (PDAS2), which has been validated against routine clinical composite indices, in routine clinical use to capture interval RA activities in the scenario of stable disease (sustained remission or LDAS) and potential intervention (prediction of flare and DMARD escalation). This study showed that patient home self-monitoring disease activity is feasible, as evident by the 92% patient completion rate and questionnaire completion at a median interval of 15.3 days, reasonably close to the intended 14 days and less than 8% of missing data in all questionnaire completions that did not affect the robustness of major findings in this study. Patients in this study were verbally instructed to record PDAS2 regularly at home every two weeks or more if needed, and eventually, the median of average monitoring interval was 15 days. The intervals of home monitoring in RA studies varied widely: ranging from one day in a reliability study on PGA, pain and fatigue (23), to one week in a web application monitoring using RAPID3/4 scores (24), one month in a tight control study using online RADAI, HAQ and VAS fatigue scores (25), and one to two months according to the protocol in a randomized controlled trial studying telemonitoring intensive strategy in early RA (26).

CUMULATIVE PDAS2

Cumulative PDAS2 (cPDAS2) integrates serial patient assessments over the entire study period and helps to show that intra-observer (patient) variability was minimal in stable conditions such as sustained Boolean or SDAI remission between two visits, or DAS28, SDAI or CDAI remission or LDAS at the second visit. For predicting SDAI flare, ΔcPDAS2 appeared to perform better than cPDAS2, and it would be useful to screen out possible flares as NPV was 88%. The major finding of practical implication from this study was that cPDAS2 and/or ΔcPDAS2 criteria predicted rheumatologists' decision to escalate DMARD, especially in those in persistent moderate/high activities and those who had a flare respectively. This, combined with flare prediction, demonstrated that cPDAS2 and ΔcPDAS2 possessed the potential in identifying the more needy RA patients who should be prioritized to be reviewed by rheumatologists earlier than scheduled visit. cPADS2 above two-visit PDAS2 mean might also have the potential to describe recent or longstanding flares and the preferential use of steroid for short-lasting flares. On the other hand, patients in remission or LDAS can be reassured if their ΔcPDAS2 remains <0.29. In both ends of RA activity spectrum, tight control of treat-to-target RA treatment strategy can be implemented in a more precise, timely and cost-effective manner. Although the likelihood ratios in this study were not in the range of those of diagnostic tests (e.g. LR+ over 10 or LR– less than 0.2) (27), nevertheless conceptually and statistically, cPDAS2 should serve as a screening tool instead of a substitution for rheumatologists' assessment and treatment decision. cPDAS2 carries a significant impact on healthcare delivery model with regards to precision medicine, big data monitoring, proactive screening for flare, remote telemedicine consultation, assessment by rheumatology

nurses and improving efficiency in manpower and resource-constrained healthcare system.

The definition of flare in this study was pragmatically taken as SDAI status shifting from remission or LDA to moderate or high activity, indicating there was a need to escalate DMARD to achieve treat-to-target. There were attempts to characterize RA flares from both patients' and physicians' perspectives, e.g. FLARE-RA self-administered tool to detect recent or current flare (28), two units of CDAI increment as minimal clinically important difference corresponding to worsening among RA patients who achieved low disease activity (29) and SDAI value at 16.7 (moderate activity range) derived from a cross-sectional study using RAPID3 questionnaire (30) (coincidentally in our study, the median SDAI of those patients whose rheumatologists decided to escalate DMARD was 16.6). Indeed, SDAI appeared to be better than DAS28(CRP) or DAS28(ESR) in discriminating the decision of modifying DMARD therapy in a prospective study (31): DAS28(ESR)=4.2 (sensitivity 87%, specificity 70%); DAS28(CRP)=3.6 (sensitivity 86%, specificity 78%); and SDAI=15 (sensitivity 90%, specificity 86%). Comparatively, in this study, the median SDAI of patients whose rheumatologists intended to escalate DMARD at the second visit was 20.6 versus 12.3 in those patients who were not considered DMARD escalation. However, these single time-point assessments would not be able to differentiate between transient self-limiting flares from sustained flares which should be flagged and prioritized for earlier medical care. On the other hand, a study of 26 non-remission RA patients taking weekly RAPID4/5 scores at home over six months showed wide fluctuations of scores, and that the clinical status during clinic visits did not

consistently reflect the clinical status over the previous few months (32). In this regard, our cumulative disease activity concept addresses the time dimension and intention to intervene i.e. DMARD escalation. Indeed, even in trials involving assessor-based outcomes, AUC was more sensitive than end-of-study outcome when there was a rapid change of medication (33).

Ambulatory patient-based RA activity reporting may facilitate the shared decision of DMARD escalation which is emphasised in RA treatment guidelines (1, 21) and this study specifically captured the rheumatologists' intention and patients' refusal. A study of 1107 RA patients showed that the adjusted attributable risk fractions for DMARD intensification were higher for patient-reported outcomes (61%) (high PGA) than doctor-reported outcomes (42%) (tender and swollen joint counts) (34). In addition, cPDAS2 possesses the ability to aggregate patient-reported outcome data over time, and it would be interesting to explore in future studies if this would pose an advantage over patient-reported outcome recorded just in the clinic, regarding any additional benefits on predicting rheumatologists' intention regarding short-lived or longstanding flares and also in early RA where there are rapid changes in disease activities and DMARD adjustments. Furthermore, there is evidence that self-reported flares, rather than short flares recorded at clinic visits, predicted radiographic structural damage (35) and a recent systematic review concluded that baseline patient reported outcomes are more consistent predictors of long-term disability than laboratory, imaging or joint count data in patients with early inflammatory arthritis (36). Further studies should also look into the consistency of

predictive power of cPDAS2 in subsequent visits within an individual patient and at group level.

Combining levels and change will increase specificity at the expense of sensitivity, and hence will bring forward patients whose rheumatologists are likely to escalate DMARD. On the other hand, using the individual level or level change will give better sensitivity at the expense of specificity, and this will help to catch more patients to be further evaluated by rheumatology specialty nurse or rheumatologists for DMARD review to tackle a potential RA flare. The data had been reviewed with the participating rheumatologists at our centre and the overall impression of over- or under-treatment with DMARD was not a major issue. Our rheumatologists valued the tool being able to identify patients with a potential flare to attend clinic earlier, as the follow-up interval between clinics could take up to half a year normally.

Our cohort comprised mostly established RA patients with a spectrum of activities and substantial change of activity between two visits. This composition was similar to studies mentioned (28-30, 32, 33). HAQ is a key component of PDAS2 and patients with longstanding RA, compared to early RA, may have a smaller change in HAQ score (37). This flooring effect was partially overcome by measuring both cPDAS2 and ΔcPDAS2.

Calculation of PDAS2 score would require computation, in contrast to RAPID3 score which could be obtained by mental calculation (38). However, this difference will be insignificant when PDAS2 assessment can be done electronically e.g.

smartphone application or web-based which may also have functionalities such as time stamp, data storage, instant calculation of cPDAS2 and ΔcPDAS2 to trigger patients' attention to advance an appointment for flare and potential DMARD escalation, and to inform health care provider. PDAS2 performance should be tested in similar telemonitoring settings, in both early RA patients who are expected to have rapid and frequent drug titration, as well as established RA patients who might have hand deformities hampering their usage of electronic devices. This is the first study that has evaluated the use of patient reported outcome measures (PROM) at home. Other PROM may also be useful. However, it is beyond the scope of this study to compare performance of different PROM in this setting.

In conclusion, this study shows that patient-based time-integrated cPDAS2 is feasible and useful in informing remission, predicting flares and the need for DMARD escalation. Further longitudinal studies are needed to assess the usefulness of cPDAS2 in subsequent visits.

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Color should be used for Figures 1-5 in print.

REFERENCES

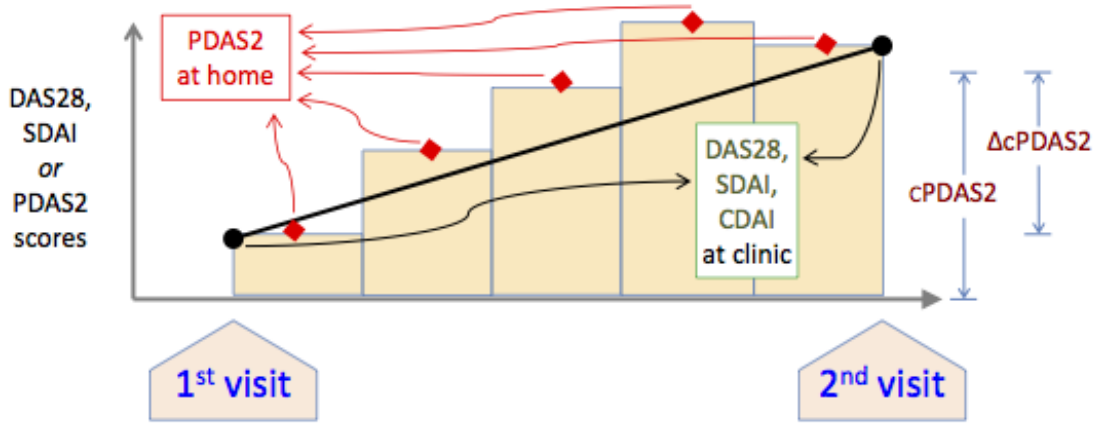
1. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
2. Smolen JS, Landewe RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020 Feb 7, pii.
3. Salaffi F, Carotti M, Ciapetti A, Gasparini S, Filippucci E, Grassi W. Relationship between time-integrated disease activity estimated by DAS28-CRP and radiographic progression of anatomical damage in patients with early rheumatoid arthritis. BMC Musculoskelet Disord. 2011;12:120.
4. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum. 2004;50(1):36-42.
5. Bykerk VP, Bingham CO, Choy EH, Lin D, Alten R, Christensen R, et al. Identifying flares in rheumatoid arthritis: reliability and construct validation of the OMERACT RA Flare Core Domain Set. RMD Open. 2016;2(1):e000225.
6. Myasoedova E, Chandran A, Ilhan B, Major BT, Michet CJ, Matteson EL, et al. The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. Ann Rheum Dis. 2016;75(3):560-5.
7. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38(1):44-8.
8. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford). 2003;42(2):244-57.
9. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7(4):R796-806.
10. Choy EH, Khoshaba B, Cooper D, MacGregor A, Scott DL. Development and validation of a patient-based disease activity score in rheumatoid arthritis that can be used in clinical trials and routine practice. Arthritis and rheumatism. 2008;59(2):192-9.
11. Scott DL, Choy EH, Greeves A, Isenberg D, Kassinor D, Rankin E, et al. Standardising joint assessment in rheumatoid arthritis. Clinical rheumatology. 1996;15(6):579-82.
12. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993;36(6):729-40.
13. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137-45.

14. Leung AMH, Farewell D, Lau CS, Choy EHS. Defining criteria for rheumatoid arthritis patient-derived disease activity score that correspond to Disease Activity Score 28 and Clinical Disease Activity Index based disease states and response criteria. Rheumatology. 2016;55(11):1954-8.
15. McGuire H, Longson D, Adler A, Farmer A, Lewin I, Guideline Development G. Management of type 2 diabetes in adults: summary of updated NICE guidance. BMJ. 2016;353:i1575.
16. Angeli F, Reboldi G, Poltronieri C, Bartolini C, D'Ambrosio C, de Filippo V, et al. Clinical utility of ambulatory blood pressure monitoring in the management of hypertension. Expert Rev Cardiovasc Ther. 2014;12(5):623-34.
17. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.
18. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
19. Green SB. How Many Subjects Does It Take To Do A Regression Analysis. Multivariate Behav Res. 1991;26(3):499-510.
20. Leung MH, Choy E, Lau CS. Validation of a patient-derived disease activity score (PDAS) in Hong Kong Chinese Rheumatoid Arthritis (RA) patients. International journal of rheumatic diseases. 2016;19 (Suppl. 2):181-2.
21. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-77.
22. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LHD, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis and rheumatism. 2011;63(3):573-86.
23. Studenic P, Stamm T, Smolen JS, Aletaha D. Reliability of patient-reported outcomes in rheumatoid arthritis patients: an observational prospective study. Rheumatology (Oxford). 2016;55(1):41-8.
24. Walker UA, Mueller RB, Jaeger VK, Theiler R, Forster A, Dufner P, et al. Disease activity dynamics in rheumatoid arthritis: patients' self-assessment of disease activity via WebApp. Rheumatology (Oxford). 2017;56(10):1707-12.
25. Walter MJ, Mohd Din SH, Hazes JM, Lesaffre E, Barendregt PJ, Luime JJ. Is tightly controlled disease activity possible with online patient-reported outcomes? The Journal of rheumatology. 2014;41(4):640-7.
26. Salaffi F, Carotti M, Ciapetti A, Di Carlo M, Gasparini S, Farah S, et al. Effectiveness of a telemonitoring intensive strategy in early rheumatoid arthritis: comparison with the conventional management approach. BMC musculoskeletal disorders. 2016;17:146-.
27. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ. 2004;329(7458):168-9.

28. Fautrel B, Morel J, Berthelot JM, Constantin A, De Bandt M, Gaudin P, et al. Validation of FLARE-RA, a Self-Administered Tool to Detect Recent or Current Rheumatoid Arthritis Flare. Arthritis Rheumatol. 2017;69(2):309-19.
29. Curtis JR, Yang S, Chen L, Pope JE, Keystone EC, Haraoui B, et al. Determining the Minimally Important Difference in the Clinical Disease Activity Index for Improvement and Worsening in Early Rheumatoid Arthritis Patients. Arthritis Care & Research. 2015;67(10):1345-53.
30. Bossert M, Prati C, Vidal C, Bongain S, Toussirot É, Wendling D. Evaluation of self-report questionnaires for assessing rheumatoid arthritis activity: A cross-sectional study of RAPID3 and RADAI5 and flare detection in 200 patients. Joint Bone Spine. 2012;79(1):57-62.
31. Soubrier M, Zerkak D, Gossec L, Ayral X, Roux C, Dougados M. Which variables best predict change in rheumatoid arthritis therapy in daily clinical practice? J Rheumatol. 2006;33(7):1243-6.
32. Blanchais A, Berthelot JM, Fontenoy AM, le Goff B, Maugars Y. Weekly home self-assessment of RAPID-4/3 scores in rheumatoid arthritis: A 6-month study in 26 patients. Joint Bone Spine. 2010;77(6):582-7.
33. Pham B, Cranney A, Boers M, Verhoeven AC, Wells G, Tugwell P. Validity of area-under-the-curve analysis to summarize effect in rheumatoid arthritis clinical trials. The Journal of rheumatology. 1999;26(3):712-6.
34. Dougados M, Nataf H, Steinberg G, Rouanet S, Falissard B. Relative importance of doctor-reported outcomes vs patient-reported outcomes in DMARD intensification for rheumatoid arthritis: the DUO study. Rheumatology (Oxford, England). 2013;52(2):391-9.
35. Ometto F, Raffeiner B, Bernardi L, Bostsios C, Veronese N, Punzi L, et al. Self-reported flares are predictors of radiographic progression in rheumatoid arthritis patients in 28-joint disease activity score remission: a 24-month observational study. Arthritis Research & Therapy. 2016;18(1):89-.
36. Gwinnutt JM, Sharp CA, Symmons DPM, Lunt M, Verstappen SMM. Baseline patient reported outcomes are more consistent predictors of long-term functional disability than laboratory, imaging or joint count data in patients with early inflammatory arthritis: A systematic review. Semin Arthritis Rheum. 2018;48(3):384-98.
37. Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. Annals of the rheumatic diseases. 2008;67(2):238-43.
38. Pincus T, Swearingen CJ, Bergman MJ, Colglazier CL, Kaell AT, Kunath AM, et al. RAPID3 (Routine Assessment of Patient Index Data) on an MDHAQ (Multidimensional Health Assessment Questionnaire): agreement with DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) activity categories, scored in five versus more than. Arthritis care & research. 2010;62(2):181-9.

Figure 1.

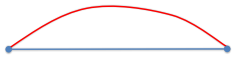
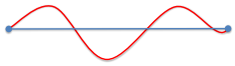
Schematic representation of the concept of cPDAS2



At the first and second visits, rheumatologists documented DAS28 (Disease Activity Score 28), SDAI (Simplified Disease Activity Index) and CDAI (Clinical Disease Activity Index) and as a routine clinical care, patients completed a questionnaire from which PDAS2 (Patient-based Disease Activity Score 2) were calculated. Between the two visits, patients completed the same questionnaires fortnightly. The area-under-curve value of these PDAS2 scores is cumulative PDAS2 (cPDAS2), and the difference between cPDAS2 and PDAS2 score at the first visit is ΔcPDAS2.

Figure 2.

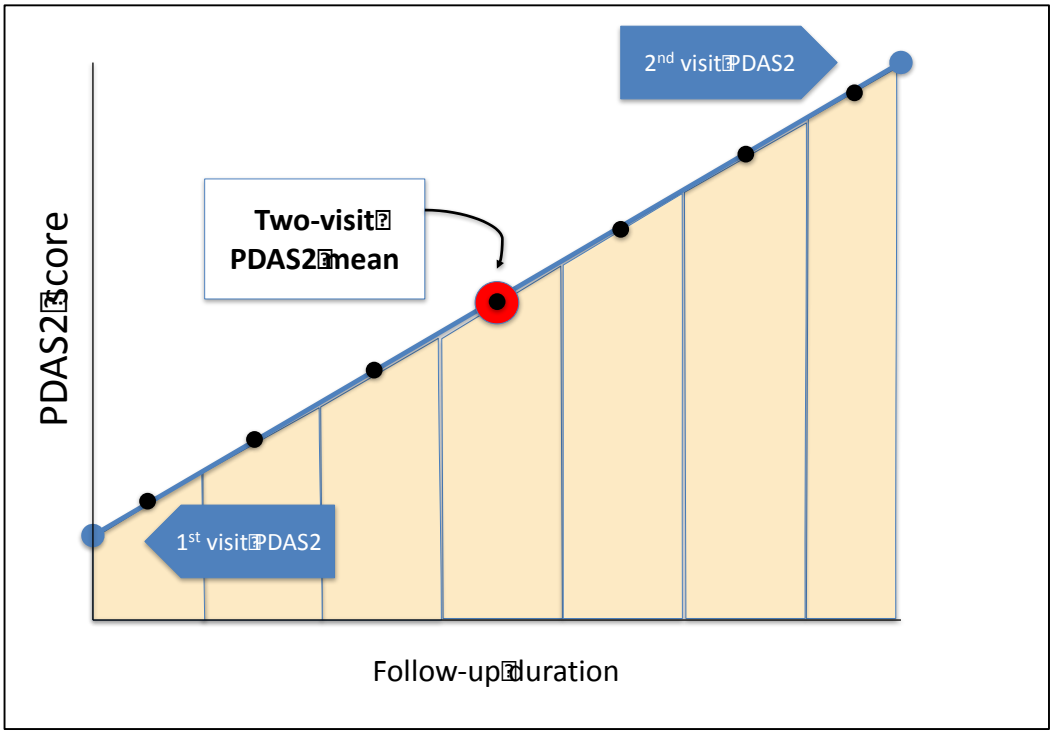
Different courses of rheumatoid arthritis activity as reflected by cPDAS2 and standard deviations of home PDAS2 readings, for a patient with identical disease activity states recorded in both clinic visits

Pattern of home PDAS2 scores (red line)	**Description**	**cPDAS2**	**Home PDAS2 scores SD**
	Sustained remission or persistent activity throughout	Same as PDAS2 in both visits	zero
	Flare between two visits, but transient	Greater than PDAS2 in both visits	↑
	Improvement between two visits, but transient	Smaller than PDAS2 in both visits	↑
	Fluctuations between two visits	Similar to PDAS2 in both visits	↑↑

Patient's PDAS2 scores in both first and second visits in blue and are static. Patient's home PDAS2 scores in red. **SD**: standard deviation.

Figure 3a

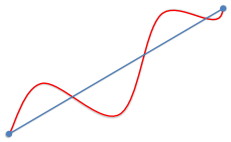
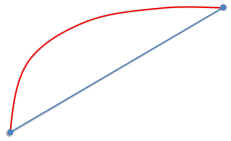
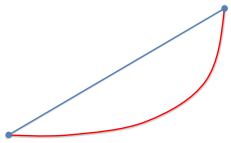
Graphical explanation on the equivalence of the two-visit PDAS2 mean and cPDAS2 if PDAS2 scores increase uniformly over time



Black dots represent average of two consecutive home PDAS2 scores

Figure 3b

Different temporal patterns of home PDAS2 changes in a flare between the first and second clinic visits

Pattern of home PDAS2 scores (red line)	Description	Home PDAS2 scores SD	ΔcPDAS2	cPDAS2 above two-visit PDAS2 mean
	Plentiful fluctuations, overall trend is flare	↑↑	↑↑	Around zero
	"Early onset" flare	↑	↑↑↑	Positive
	Recent or "late onset" flare	↑	↑	Negative

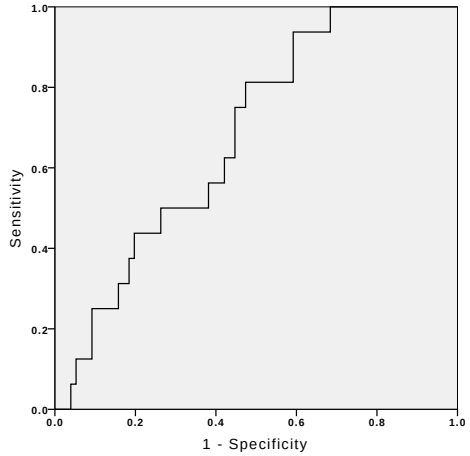
Patient's PDAS2 scores in both first and second visits in blue and are static. Patient's home PDAS2 scores in red. SD: standard deviation.

Figure 4

Receiver operating characteristic curves

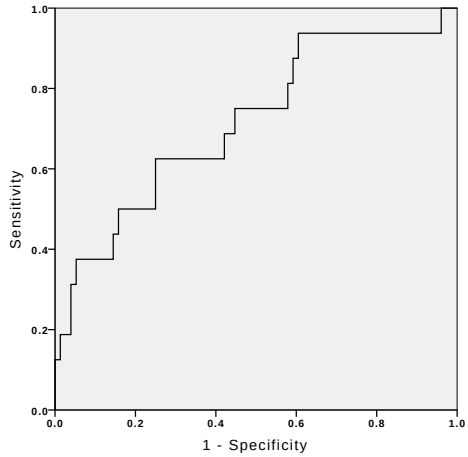
4a. ΔcPDAS2 to predict Simplified Disease Activity Index flare from remission/low disease activity to moderate/high disease activity

P=0.04, Area under curve=0.71 (95% CI: 0.57, 0.84)



4b. (cPDAS2 ≥ 4.33 and ΔcPDAS2 ≥ 0.059) to predict rheumatologist's decision to escalate disease modifying anti-rheumatic drugs (DMARD)

P=0.007, Area under curve=0.72 (95% CI: 0.57, 0.86)



4c. (cPDAS2 ≥ 4.33 or ΔcPDAS2 ≥ 0.059) to predict rheumatologist's decision to escalate disease modifying DMARD

P=0.02, Area under curve=0.68 (95% CI: 0.56, 0.80)

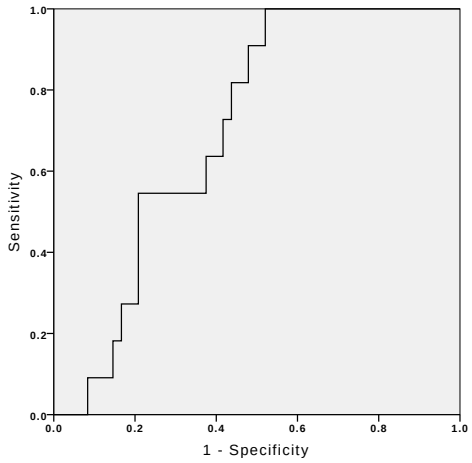
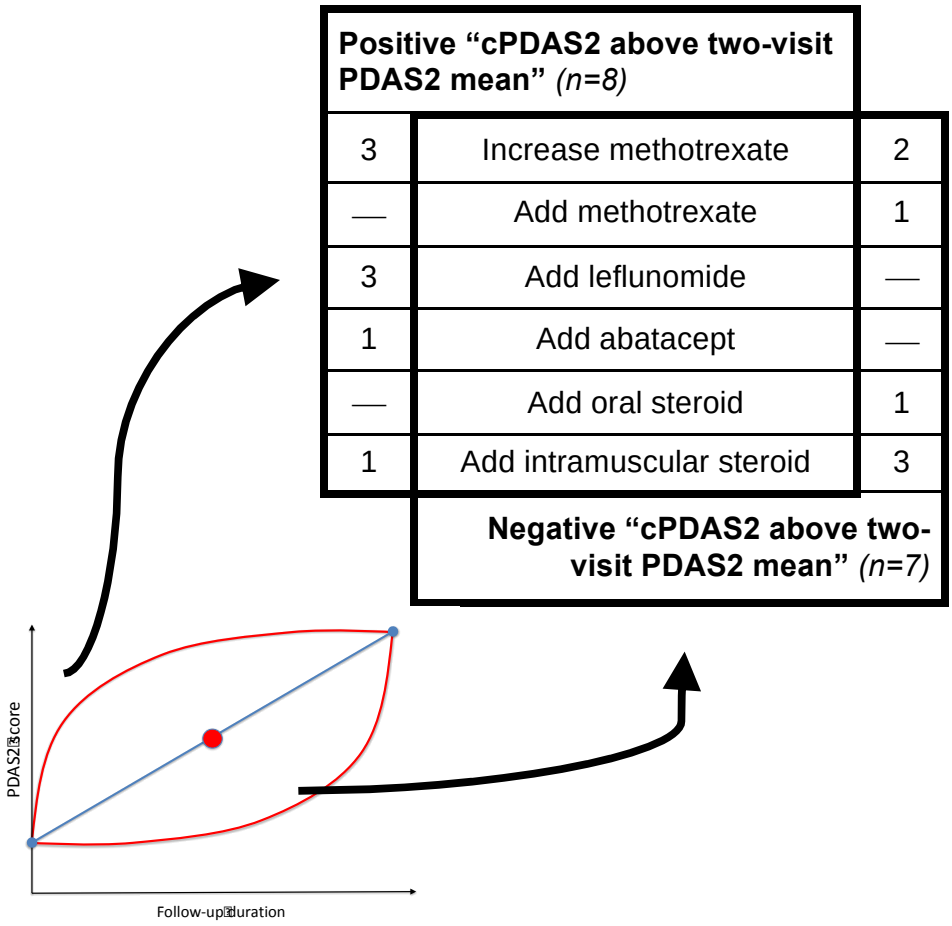


Figure 5

The nature of DMARD escalation and positive or negative values of cPDAS2 above two-visit PDAS2 mean



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