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Value of RAPID3 in patients with PsA: results from the TICOPA and LOPAS II databases

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Objective: To analyze RAPID3, a patient-reported, composite index, designed initially for feasibility in clinical care. RAPID3 was developed in rheumatoid arthritis, but has been found useful in many rheumatic diseases. We analysed RAPID3 in patients with psoriatic arthritis (PsA).

Methods: Post-hoc analyses were performed on two independent datasets, the tight control of PsA (TICOPA) clinical trial, and the long-term outcome in PsA study (LOPAS II), an observational cohort. RAPID3 (0-30) is the total of three 0-10 scores for HAQ-DI (recalculated from 0-3), pain visual analog scale (VAS), and global VAS. RAPID3 scores were compared to the PsA disease activity score (PASDAS) and disease activity in psoriatic arthritis (DAPSA) and other available clinical measures, according to Spearman correlation coefficients, standardised response mean (SRM), standard error of the mean (SEM), smallest detectible difference (SDD), minimally important difference (MID in patients who improved) and receiver-operating characteristic (ROC) curves. RAPID3 remission was compared to criteria for both standard minimal disease activity (MDA) and very low disease activity (VLDA).

Results: RAPID3 was correlated significantly with PASDAS in TICOPA ($r=0.79$, $p<0.01$) and with DAPSA in LOPAS (rho=0.59, $p<0.01$), and with most other measures in both datasets. RAPID3 discriminated between tight control and standard care in TICOPA at 48 weeks at levels comparable to DAPSA and the PASDAS ($p<0.01$). RAPID3 remission discriminated treatment groups in TICOPA intermediate between MDA and VLDA criteria.

Conclusion: RAPID3 appears comparably informative to PASDAS and DAPSA in PsA, with greater feasibility for routine clinical care.

Significance and Innovation

- RAPID3 is correlated significantly with more comprehensive PsA-specific outcome measures, both those assessing arthritis (DAPSA) and global disease activity (PASDAS)
- RAPID3 can differentiate treatment groups in the TICOPA clinical trial.
- A modified RAPID3 including a skin VAS was not clearly superior in performance but levels of skin disease were low in the datasets used.
- RAPID3 remission is correlated significantly at the individual patient level with other remission measures but physical examination is still required for optimal clinical decision making.

Psoriatic arthritis (PsA) is a complex disease involving both the musculoskeletal and cutaneous systems. Many outcome measures have been developed specifically for PsA to reflect both systems, with composite indices, which may include assessment of arthritis (both peripheral and axial), enthesitis, dactylitis, skin and nail psoriasis, and patient-reported outcomes (1). Such composite indices are used widely in clinical trials, but generally not incorporated into routine practice due to their complexity(1). The only quantitative data available in routine care of many PsA (and other rheumatology) patients are laboratory tests, with significant limitations(2).

Routine assessment of patient index data 3 (RAPID3) is an index composed of only the 3 patient self-reported measures from the rheumatoid arthritis (RA) Core Data Set(3): physical function on a health assessment questionnaire (HAQ) or its multidimensional version (MDHAQ), and pain and patient global estimate on two 0-10 visual analogue scales (VAS) (4). The primary initial goal for RAPID3 was to provide a feasible quantitative index for management of RA that was comparable to DAS28 (disease activity score 28) (5) to distinguish active from control treatment in clinical trials (6). Subsequently, RAPID3 has been found informative in axial spondyloarthritis (7-10), osteoarthritis(11), gout(12) systemic lupus erythematosus(13) and other arthritides(12, 14-16).

This study assessed the potential value of RAPID3 to depict clinical status compared to PASDAS, DAPSA, and other measures in two datasets, the tight control of PsA (TICOPA) study,

a clinical trial, and the long term outcome of PsA study (LOPAS II), an observational cohort. An important consideration that RAPID3 may not address the dermatological aspects of PsA effectively was analysed using a modified RAPID3Ps, which included a fourth item, a VAS scale for skin disease activity that could be added to the original RAPID3.

Materials and Methods

Data. Post-hoc analyses were performed on two independent datasets to study the value of RAPID3 in PsA. First, we analysed data from the tight control of PsA (TICOPA) clinical trial (ClinicalTrials.gov NCT01106079, ISCRCTN30147736), to assess its performance in a controlled trial setting. Second, we used data from the long-term outcomes in PsA study (LOPAS II) to assess its performance in an observational cohort setting (17).

TICOPA trial. The TICOPA trial is a UK multicentre randomised controlled trial, in which 206 adults with early psoriatic arthritis were randomly assigned on a 1:1 ratio either to tight control with a step-up regimen aiming for minimal disease activity using methotrexate, combination disease-modifying anti-rheumatic drugs (DMARDs) and anti-tumour necrosis factor drugs as required or to standard care(18). In the TICOPA dataset, the PsA disease activity score (PASDAS) was used as the "gold standard" comparator, as this composite measure addresses all aspects of psoriatic disease(19). Differences between treatment groups according to RAPID3, PASDAS and other PsA measures were compared.

LOPAS II observational cohort. LOPAS II is a prospective, multicentre observational cohort study to investigate the effect of conventional synthetic disease modifying anti rheumatic drugs (csDMARD) and anti-Tumour Necrosis Factor inhibitors (anti-TNF) on clinical and patient reported outcomes among PsA patients of any age and disease duration who fulfilled the classification for psoriatic arthritis (CASPAR) criteria(20) and were being commenced on

csDMARD or anti-TNF as part of routine clinical care. In the LOPAS study, analyses were undertaken on participants with complete data at baseline and three months follow up. The Disease Activity in Psoriatic Arthritis (DAPSA) was used as a composite measure of articular disease (calculated from the 66/ 68 tender and swollen joints count, C reactive protein, patient global assessment and pain visual analogue scales)(21). The required items for MDA and PASDAS were not all available in this dataset.

RAPID3 index. RAPID3 scores are calculated as the 0-30 total of the three 0-10 RA core data set measures of physical function, pain, and a patient global estimate (4). Physical function is assessed on a Health Assessment Questionnaire (HAQ) (22) or multidimensional version (MDHAQ); activities are scored 0-3 and the total of 0-30 or mean 0-3, are converted to a 0-10 score. Pain and a patient global estimate were scored in these studies on a (0 -10) visual analog scale (VAS) using the GRAPPA PsA global wording "In all the ways in which your psoriasis and arthritis, as a whole, affects you…". In addition, a modified RAPID3 which included a VAS scale for skin disease activity as a fourth item was studied, because of consideration that the 3-item RAPID3 would not be informative concerning the dermatological aspects of PsA.

The range for RAPID3 is 0-30 and severity categories have been defined for RA: ≤3 for remission, 3.1-6.0 for low, 6.1-12.0 for moderate, and >12 for high severity (23). These potential categories were studied in comparison with other remission and low disease categories from PsA specific measures, at both group and individual levels. RAPID3 remission was compared to both the standard Minimal Disease Activity (MDA) criteria(24) and the very low disease activity (VLDA) criteria(25), which were developed specifically for

PsA and have been shown to be correlated significantly well with other disease activity measures(26, 27) in PsA. MDA also is associated with physician and patient opinion of low disease activity using anchor questions(25), and has prognostic value for better functional outcome and lower rates of radiographic damage(28). The MDA criteria for PsA require meeting 5 of 7 cut points in 7 measures: HAQ≤0.5, patient global VAS≤20mm, patient pain VAS≤15mm (the three RAPID measures, though at different cut-points); tender joint count (TJC)≤1; swollen joint count (SJC) ≤1; enthesitis count ≤1 and psoriasis area and severity index (PASI) ≤1 or body surface area (BSA) ≤3(24). To meet VLDA criteria, all seven cut points must be met (25). This endpoint has been investigated in view of the emphasis on remission as the ideal target for treatment(29); preliminary validation has indicated that it is a very stringent measure(25). A more stringent method to assess remission based on RAPID3, with addition of whether a patient has 0 or1 vs >1 swollen joint (RAPID3SJC1)(30, 31) also was analysed

In studies of LOPAS II data, construct validity was assessed using Spearman correlation coefficients with other disease outcome measures. Agreement between the DAPSA and RAPID3 was determined on a Bland Altman plot(32) (after rescaling both measures to allow comparison on the same plot). Responsiveness was assessed using Standard Error of the Mean (SEM), Standardised Response Mean (SRM) and Smallest Detectible Difference (SDD). The Minimally Important Difference (MID) was determined using the health based anchor method (mean change in score amongst patients who improved) and Receiver Operator Characteristic Curve (ROC) methods (the change in score at the top left corner of the curve representing the smallest amount of misclassification). Responsiveness of the measures as

continuous variables and their correlations with other disease activity measures were assessed in both cohorts

Results

TICOPA clinical trial. In the TICOPA study, the disease duration of patients was less than 24 months and their mean age was 44 years. RAPID3 scores were correlated significantly with PASDAS (Spearman's correlation 0.80, $p<0.01$) at all baseline and follow up visits (figure 1), indicating construct validity. RAPID3Ps (which includes a skin VAS) was also correlated highly with PASDAS at similar levels. The change in score at follow up was also correlated significantly with the change in PASDAS (0.64, $p<0.01$).

RAPID3 was highly discriminant of change in the tight control vs standard treatment groups (Table 1). (t value -3.43, $p<0.01$) and superior to each individual measure. Patient-reported measures were more discriminant than joint counts (Table 1). RAPID3 also was similar in discrimination to the disease activity in PsA (DAPSA) score, but slightly less than PASDAS (table 2). When plotting mean scores for both PASDAS and RAPID3 in the TICOPA trial, similar responses are seen at each time point (figure S1).

The proportions of patients who were classified as in remission according to RAPID3 and RAPID3SJC1 lies between MDA and VLDA (table 2), as might be expected. RAPID3 NR and RAPID3SJC1 in TICOPA also were highly discriminant between treatment groups (table 2), although slightly lower than MDA and DAPSA remission. At an individual (rather than group) level, exact agreement between MDA and RAPID3 remission was seen in 85.2% of patients at 48 weeks. Only five patients (of 67) in RAPID3 remission were not in MDA due to higher physician assessed disease activity. By contrast, 22 patients were in MDA but did not meet

the RAPID3 remission levels due to high patient reported measures. The majority of patients (58 of 67) in RAPID3 remission also met the more stringent RAPID3SJC1 criteria (RAPID3 remission + SJC≤1)(30, 31).

Agreement between RAPID3 remission and VLDA was slightly lower than MDA (percentage exact agreement (PEA) of 73.6%). Compared to this more stringent target, 44 of the 67 patients in RAPID3 remission were not in VLDA whilst only four patients were in VLDA but did not meet RAPID3 NR due to high patient reported measures. This finding suggests that the RAPID3 remission cut off lies between MDA and VLDA in terms of disease activity cut off. For those in RAPID3 remission, the levels of residual disease activity is shown in table S1. The majority of patients have low levels of ongoing active disease including CRP which is normal in around 75% of patients.

LOPAS observational study. In the LOPAS study, the mean disease duration 5.8 years (sd 7.77) and the mean age was 51 years. RAPID3 scores were correlated significantly with the DAPSA composite measure (Spearman correlation coefficient 0.59, $p<0.01$) as confirmed in figure 2, and with other patient reported outcomes: Joint VAS (0.83), EQ5D (0.65), FACIT fatigue (0.63). Correlation with clinical joint count and CRP was lower: tender joint count (0.39), swollen joint count (0.21), CRP (0.17). No significant difference was seen between the response to treatment (within each independent treatment group) according to RAPID3 or DAPSA for either the TNF ($p= 0.76$) or DMARD ($p=0.09$) groups (Figure S1).

RAPID3 was responsive according to the mean change, SEM, SRM and SDD during follow up (Table 3). The MID for improvement using the anchor method for the RAPID3 was -8.1 (sd 5.9) and DAPSA -27.9 (sd 23.7). The MID using the ROC method (figure 3) for the RAPID3 was -5.1 (AUC 0.84) and DAPSA -16.7 (AUC 0.75). Using initiation of treatment (baseline visit) as a gold standard for active disease, only a small number of patients were potentially misclassified as being in remission or low disease activity by either score: DAPSA (2.3%) and RAPID3 (5%) (table S2). RAPID3 was correlated significantly with the EQ5D, Joint VAS and FACIT fatigue, but at lower levels with clinical joint counts and the CRP. This finding highlights some disconnect between physician and patient reported outcomes.

Discussion

These analyses indicate that RAPID3 and RAPID3Ps show good responsiveness and discrimination in PsA. In the TICOPA dataset, RAPID3 is correlated highly with the PASDAS score and is more discriminative than individual measures and the DAPSA score. In the LOPAS dataset, RAPID3 is correlated significantly with the DAPSA and had similar responsiveness. We also report an estimate of the MID for improvement and smallest detectable difference for the RAPID3 in PsA.

The RAPID3 score is a generic tool developed to assess patient status quantitatively in clinical practice. It was developed in RA and has been found of value in many rheumatic conditions, including spondyloarthritis(7-10), osteoarthritis(11), gout(12) systemic lupus erythematosus(13) and other arthritides(12, 14-16). However, in PsA, in addition to the

musculoskeletal manifestations, most patients also have skin psoriasis. In these analyses, adding a skin disease activity VAS to create the RAPID3Ps did not show a meaningful advantage over the established RAPID3 score. This may be anticipated since RAPID3 measures constitute 3 of 4 in RAPID3Ps, skin involvement was mild in these cohorts and it may be captured at least in part in the patient global assessment. In earlier studies to establish RAPID3, versions that included joint counts or physician global estimates, termed RAPID4 and RAPID5 added little incremental value to RAPID3, but required considerably more complexity (23, 33)

RAPID3 NR also performed well with the vast majority of patients who were identified as being in remission showing low levels of residual disease activity. The RAPID3 measure includes the same 3 patient reported outcomes as the MDA criteria, and cut points for the patient reported items of MDA are similar to RAPID3 remission. Since MDA requires 5 of 7 cut points, 2 patient measures may be above the cut point, explaining why RAPID3 remission appears intermediate between MDA and VLDA in stringency. Only a few cases were in RAPID3 remission but had active disease as assessed by the physician using joint counts and skin scores. Nonetheless, all measures and indices are only a guide, and a clinical assessment with a full medical history and physical examination is required for optimal clinical decisions.

The use of the HAQ as a measure of disease activity in PsA may be questioned. The HAQ primarily assesses upper limb (hand) function and was developed in RA. PsA has different musculoskeletal manifestations (enthesitis/ dactylitis, differing joint distributions such as large joint monoarthritis). Furthermore it has been suggested that HAQ function scores

become more influenced by damage than activity in established disease, potentially limiting responsiveness(34). However, despite these theoretical concerns we found RAPID3 to be sensitive to change and discriminative in early disease (TICOPA) and later disease (LOPAS), in keeping with other studies showing responsiveness of HAQ even in established disease(35, 36).

Several methodological limitations are recognized in interpreting the finding of this study. The RAPID3 was calculated from existing outcome measures collected within the two studies. Therefore the HAQ-DI was used instead of the MD-HAQ and VAS scales for pain and global disease activity were used rather than the NRS in the RAPID3 tool. We believe from previous studies that these are comparable but future research with the specific RAPID3 tool is required. To maximise feasibility in clinical practice, the use of a standard tool (RAPID3) across all diseases appears desirable. However, it must be noted that these patients were all recruited from rheumatology clinics and the average levels of skin disease were very low (TICOPA: median PASI 2.6, LOPAS II: median Dermatology Quality of Life Index – DLQI 2.0 and skin VAS 30.5/100). The absence of a skin specific measure may limit performance in a population with substantial skin disease. There were also a few patients in RAPID3 remission who had signs of active disease on clinical assessment. Thus, clinical assessment, in addition to the RAPID3 or any index, is required in all patients. Little change in radiographic damage was seen over the 48 week period of the TICOPA study, a fortunate development for patients, which limits comparison of radiographs with RAPID3. In addition, radiographs were not routinely performed in the LOPAS study. Therefore a formal comparison of changes in RAPID3 and radiographic damage is not available in this report.

We have not analysed possible influence of contextual factors or comorbidities on RAPID3. Such contextual factors as fibromyalgia are known to impact all rheumatology indices, which necessarily include at least one patient-reported measure independent of disease activity. For example, a patient who has no swollen joints and a CRP of 10mg/L, but 14 tender joints and a patient global assessment of 8 would have a DAPSA of 23 even if the physician global assessment were "0"; the RAPID3 would be 16, assuming a pain score of 8, and both indices would indicate "high activity/severity." Similar considerations pertain to most rheumatology indices, as concomitant fibromyalgia was found to be associated with higher scores by Brikman *et al* in all in composite measures including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Dermatology Life Quality Index, Leeds Enthesitis Index (LEI). Composite Psoriatic Disease Activity Index (CPDAI), MDA and DAPSA scores(37).

We emphasize again that all indices, whether RAPID3, PASDAS, DAPSA or others, must be informed by accompanying clinical, serological and imaging assessments in clinical practice. Whilst such measures should be viewed as providing valuable quantitative data which add to a standard medical history and physical examination toward optimal clinical decisions, an index should not be the only basis for a clinical decision other than in a protocol-directed research study. A final limitation is that we have not assessed the stability (test re-test reliability) of the RAPID 3 in this study, although one would anticipate reliability similar to that established in other diseases (23, 38).

We report data from two independent datasets examining the responsiveness and discrimination of RAPID3 in PsA. We also report data suggesting the addition of a skin

assessment does not improve sensitivity to change in these particular cohorts. We also report an estimate of the MID for improvement in PsA. Taken together these data support the value and validity of RAPID3 as a feasible and sensitive measure of disease activity in PsA.

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Table 1: Responsiveness of individual items and indices, ranked by t value in the TICOPA trial

Measure	Tight Control				Standard Care				T	p
	Baseline	Mean change	SRM	ES	Baseline	Mean change	SRM	ES		
PASDAS	5.27	-2.49	-1.45	-1.77	4.96	-1.38	-0.83	-1.09	-3.75	0.00
RAPID3	4.18	-2.16	-1.07	-1.06	3.59	-1.01	-0.47	-0.52	-3.43	0.00
Phys Global	44.10	-32.26	-1.57	-1.62	40.80	-19.83	-0.86	-1.27	-3.34	0.00
Pt Global	56.15	-33.60	-1.05	-1.20	51.54	-18.64	-0.56	-0.69	-3.12	0.00
pain VAS	53.42	-31.92	-1.05	-1.18	47.33	-17.79	-0.56	-0.68	-2.82	0.01
DAPSA	31.24	-19.01	-1.08	-0.94	30.04	-11.45	-0.69	-0.53	-2.61	0.01
Fatigue VAS	48.85	-21.44	-0.73	-0.78	46.39	-13.20	-0.46	-0.46	-1.84	0.07
TJC	12.33	-6.62	-0.65	-0.56	13.22	-3.34	-0.28	-0.24	-1.57	0.12
SJC	7.57	-6.27	-0.96	-0.97	6.82	-4.50	-0.57	-0.58	-1.22	0.22

DAPSA – disease activity in psoriatic arthritis, ES – effect size, PASDAS - PsA disease activity score, Phys – physician, Pt – patient, RAPID3 – routine assessment of patient index data 3, TJC – tender joint count, SJC – swollen joint count, SRM – standardised response mean, VAS – visual analogue score

Table 2: Discriminative capacity of disease activity state definitions in the TICOPA trial

Measure	TC % achieved	StdC % achieved	Chi Squared	P value
MDA	58.4	34.1	10.106	0.001
VLDA	22.5	7.3	7.603	0.006
RAPID3 near remission	44.3	25.3	7.483	0.006
RAPID3Ps near remission	75.3	63.7	2.950	0.112
RAPID3SJC1	42.2	22.9	7.303	0.009
RAPID3 near remission or mild	58.8	45.1	3.535	0.060
PASDAS low	63.9	50.5	3.432	0.064
DAPSA low (Helliwell)	76.7	65.9	2.463	0.117
DAPSA low (JS)	70.0	58.5	2.464	0.117
DAPSA remission (JS)	43.3	19.5	11.193	0.001

DAPSA – disease activity in psoriatic arthritis, MDA – minimal disease activity, RAPID3 – routine assessment of patient index data 3, PASDAS – psoriatic arthritis disease activity score, StdC – standard care, TC – tight control, TICOPA – tight control of psoriatic arthritis, VLDA – very low disease activity

Table 3 - LOPAS II Sensitivity to change of the RAPID3 with other disease outcomes

Outcome	Mean change (sd)	SEM	SRM	SDD
RAPID3	-6.2 (9.9)	6.15	0.62	8.5
DAPSA	-18.4 (30.0)	17.6	0.61	40.8
HAQ	-0.20 (0.52)	0.29	0.38	0.4
EQ5D VAS	9.0 (24.6)	13.8	0.37	19.2
FACIT-Fatigue	4.4 (9.3)	5.6	0.45	7.7
Global VAS	-18.8 (31.7)	19.5	0.59	27.1
Pain VAS	-17.2 (30.1)	18.5	0.57	25.6
Joint VAS	-17.2 (31.4)	18.0	0.54	24.9
Skin VAS	-11.2 (31.1)	17.5	0.36	24.2

Figure 1 - Correlation between PASDAS and RAPID3 and RAPID3Ps scores at all key visits in TICOPA (Spearman's rho 0.80, $p<0.01$ and 0.82, $p<0.01$)

Figure 2 - Bland Altman Plot of DAPSA/ RAPID3 in LOPAS2 dataset

Figure 3 - Receiver Operator Curves of DAPSA and RAPID 3 in the LOPAS dataset