Use of rheumatoid arthritis impact of disease (RAID) in routine care; identification of DAS28 remission and unmet patient reported outcomes.

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Objectives

To assess how the patient reported outcome RAID relates to DAS28 categories in routine care, it’s utility identifying patients in DAS28 remission (RDAS) or low disease activity (LDAS) and the burden of unmet patient reported needs in those achieving RDAS/LDAS.

Methods

DAS28 and RAID scores were collected from patients with established RA attending for routine review. Relation between RAID and DAS28 assessed with univariate pairwise correlation and mixed-effects linear regression analyses. RAID <2 is defined as a patient acceptable state.

Results

198 patients were assessed, with 220 observations. Using DAS28-CRP categories: 47.5% RDAS, 14.1% LDAS, 31.8% moderate DAS (MDAS) and 6.6% high DAS (HDAS). Both patient VAS and tender joint count were highly statistically associated with RAID using linear regression (p<0.0001). Mean RAID score per DAS28-CRP category was RDAS 1.84, LDAS 4.78, MDAS 5.60, HDAS 7.68, with a statistically significant increase in RAID per unit increase in DAS-CRP or DAS28-ESR on linear regression (p<0.001). Of 66 patients with RAID <2, 64 (97%) were in RDAS and 65 (98.5%) in RDAS/LDAS. Of 134 patients in RDAS/LDAS, RAID was ≥2 in 69 (51.5%) with fatigue and sleep being the worst scoring domains.

Conclusion

RAID functions well as a PRO in routine care. Patients with RAID <2 are highly likely to be in RDAS/LDAS, and if pre-screened could avoid a clinic visit. Analysis of RAID domains provides individualised targets for holistic care in RA management, with fatigue and sleep problems dominating unmet needs in those in RDAS/LDAS.

Keywords

Rheumatoid arthritis
Disease activity score
RAID
Patient reported outcomes

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Key messages

1. RAID functions well in routine care and associates closely with subjective components of DAS28
2. Patients with a RAID score <2 are highly likely to be in RDAS or LDAS
3. Fatigue and sleep are the worst scoring domains in R/LDAS patients with a RAID >2
Introduction

Treat-to-target (T2T) principles are widely recognised as the best strategy to achieve optimal disease outcomes in rheumatoid arthritis (RA) (1). Two target outcomes are proposed within both ACR and EULAR guidelines (2, 3) and these have been endorsed by national bodies such as NICE (4). These targets, either remission or low disease activity, are based on the DAS28 composite score which includes observer, laboratory and patient reported assessments of disease activity.

Inflammation in RA has been clearly linked to joint damage and adverse cardiovascular outcomes, and in broad terms new therapies and treatment strategies have been successful in suppressing both inflammation and its consequences (5,6). However, it has become increasingly clear that advances in RA management have had less impact on some patient reported outcomes (PRO), such as fatigue, pain, depression, work performance and health related quality of life (7,8,9).

Given the discordance in RA outcomes assessed by composite measures based on inflammation versus PROs, it is evident that to be truly holistic the management of RA in a T2T context should include assessment of both aspects (inflammation and PRO) in routine practice. DAS28 and SDAI provide assessments based on observer, patient and laboratory assessments. A variety of composite PROs are available to complement these, such as RAID, RADAI-5 and RAPID3. The RAID score is a patient derived differentially weighted seven item tool assessing pain, functional disability, fatigue, sleep, coping, physical and emotional well-being. It has been validated, is reliable, sensitive to change and eular adopted (10, 11). It correlates well with RADAI, patient global measures, SF36 physical and mental subscales, EQ5D and the DAS28 score (10, 12, 13). On an individual patient level a score below 2 is deemed a patient acceptable state (14, 15) and both absolute and relative minimally clinical important improvements are also defined (14).

In an increasingly over populated and time constrained healthcare service, a particular attraction of RAID is its simplicity, with applicability to at-home patient completion and submission electronically, potentially avoiding the need for a face to face consultation. We have therefore assessed the utility of RAID in routine care as a tool to identify patients in DAS28 remission (RDAS) or low disease activity (LDAS) and to reveal the burden of unmet patient needs in those achieving RDAS/LDAS.
Methods

Patients attending for routine RA review at St George’s University Hospitals NHS Foundation Trust were assessed by a rheumatologist, nurse practitioner or physician assistant. Data collected at each clinic visit included the DAS28 score, acute phase reactants and the RAID questionnaire. All data were collected as standard routine care practice. Patients gave verbal consent to pooled retrospective data analysis.

The RAID score was calculated using the on line eular toolkit (11). Each of the 7 individual domains of the RAID is scored on a 10 item numerical rating scale (NRS), with 0 being a good or low activity score and 10 a high or severe activity score. In the absence of guidance we arbitrarily classified the NRS results into one of three equivalent sized ranges (mild 0-2, moderate 3-6, severe 7-10) to give an overall idea which domains scored particularly poorly or well.

The DAS28-ESR thresholds for remission (<2.6), low (2.6 – 3.2), moderate (3.3 – 5.1) and high (>5.1) disease activity were used, whereas for DAS28-CRP adjusted thresholds were adopted, remission (<2.4), low (2.4-2.9), moderate (2.91-4.6) and high (>4.6) disease activity respectively (16).

Seropositive status was defined as testing positive for either RF or ACPA, or both. Only those that tested negative for both RF and ACPA were defined as seronegative.

The relationship between RAID scores with both DAS28-CRP and DAS28-ESR and their sub-components was initially explored descriptively by comparing mean scores and univariate pairwise correlation analysis. The swollen joint count (SJC) and tender joint count (TJC) scores were square-root transformed, whilst the ESR and CRP were log-transformed to match their form used in the DAS28 formulation. The relationship between each sub-component of the DAS28 and the RAID score was explored using mixed-effects linear regression. Mixed-effects regression allows multiple observations per patient to be modelled, accounting for the likely correlation due to non-independence within these observations. The model included all sub-components of the DAS28, and controlled for important confounders including age, sex and seropositive status. The analyses were conducted separately for the DAS28-CRP and DAS28-ESR. All analyses were conducted using Stata version 15.
Results

198 patients with established RA were assessed, contributing 220 observations. The sample was 80.8% female, mean age 59.0 years, 72.2% RF positive and 77.8% ACPA positive. 84.8% of patients tested positive for either RF or ACPA (or both) and were defined as seropositive RA. Patients were on a range of therapies including csDMARDs and bDMARDs, managed according to standard care.

DAS28-CRP was available for all 198 patients. The number in remission (RDAS) at first observation was 94 (47.5%), low disease activity (LDAS) 28, 14.1%, moderate disease activity (MDAS) 63, 31.8% and high disease activity (HDAS) 13, 6.6%. The distribution per DAS28-ESR category was similar with RDAS 46.7%, LDAS 16.8%, MDAS 29.4%, HDAS 7.1%.

RAID scores were recorded 218 times from 196 patients, with a mean of 3.87 (SD 2.55), range 0 – 9.64. Patients reported no difficulties understanding or completing the questions, taking less than 5 minutes. Only 2 questionnaires (1%) had missing data. The requirement to complete the RAID questionnaire during the consultation caused no delays to the normal conduct and running of the clinics.

Figure 1 shows the relation between RAID scores and DAS28-CRP, Spearman correlation 0.78. RAID scores also correlated strongly with DAS28-ESR (r=0.75) and patient global VAS (r=0.83), but less well with square-root TJC (r=0.55), square-root SJC (r=0.39), log ESR (r=0.38) and log CRP (r=0.30).

Using multiple mixed-effects linear regression, both the patient global VAS and the square-root TJC were highly statistically significantly associated with RAID scores (P<0.01), where high TJC and PGA associate with increased scores on the RAID. Standardised coefficients indicate that the patient global VAS had the largest association at 0.65, followed by TJC at 0.23. Additionally, the log CRP indicated statistical significance at P=0.048, although the level and comparative effect were small relative to the TJC and PGA, with a standardised coefficient of 0.08. The results are provided in Supplementary Table S1, available at Rheumatology Advances in Practice online.

The mean RAID score per DAS28-CRP disease activity category was RDAS 1.84 (SD 1.55), LDAS 4.78 (SD 1.73), MDAS 5.60 (SD 1.63) and HDAS 7.68 (SD 1.29), see Supplementary
When modelled using mixed effects linear regression, whilst controlling for age, sex and seropositivity, there was a statistically significant increase in RAID scores for each one unit increase in DAS28-CRP score ($\beta = 1.76$; 95% Confidence Intervals 1.59 – 1.94, P<0.001). Similarly when DAS28-ESR is modelled in a mixed effects linear regression, controlling for age, sex and seropositivity, there was a statistically significant increase in RAID scores for each one unit increase in DAS28-ESR ($\beta = 1.43$; 95% Confidence Intervals 1.28 – 1.58, P< 0.001) with mean RAID score per DAS28-ESR disease activity category, RDAS 2.14 (SD 1.93), LDAS 4.16 (SD 1.96), MDAS 5.52 (SD 1.62) and HDAS 7.52 (SD 1.59).

Of 66 patients with RAID <2 (patient acceptable state), DAS28-CRP was <2.4 in 64 (97%) and ≤2.9 in 65 (98.5%), and similarly DAS28-ESR was < 2.6 in 61 (92.4%) and ≤3.2 in 65 (98.5%).

Of 105 with DAS28-CRP <2.4 (remission) RAID was ≥2 in 41 (39%), and of 134 patients with DAS28-CRP ≤2.9 (remission and low disease activity) RAID was ≥2 in 69 (51.5%). Figure 2 shows the proportion of patients with DAS28-CRP ≤2.9 and RAID ≥2 scoring mild (0-2), moderate (3-6) and severe (7-10) for each domain of the RAID questionnaire. The domains with the largest proportion of these patients scoring in the severe range were fatigue 35.6%, sleep 33.3% and emotional well-being 28.9%. None of the seven domains scored uniformly well, the best being functional disability and coping where 35.6% and 33.3% of patients respectively scored 0 – 2 on these domains.

**Discussion**

This is the first report of the utility of the RAID PRO measure in a routine care setting in UK practice. The score correlates well with the total DAS28-CRP or DAS28-ESR scores and also with patient global assessment and TJC, but not with SJC, CRP or ESR, as found by others (10, 12), and in keeping with this being a patient derived outcome, rather than a measure of inflammation. Significant differences in RAID scores between patients in RDAS, LDAS, MDAS and HDAS categories, whether using DAS28-CRP or DAS28-ESR confirm previous reports that there are significant differences in PROs between these categories, including remission and low disease activity in early RA (17,18). Our findings in a mixed population of patients with
established RA under routine review add support to remission being a preferable goal compared to low disease activity in T2T terms.

A very practical utility of RAID in routine care is apparent from the fact that virtually all patients with a RAID <2, defined as a patient acceptable state (14,15) were also either in RDAS or LDAS. As such if the RAID score is <2 it may be confidently assumed that the patient has also achieved a DAS28 T2T goal. If developed as an ‘at home’ tool, for example via an ‘app’ the RAID could function as a triage tool, potentially avoiding the need for a face to face disease activity assessment in the clinic. This would be an innovative advance in an over-populated resource limited healthcare system, where priority is better given to those RA patients with unsuppressed disease activity, requiring active treatment changes.

In contrast, where the RAID is >2 the range of DAS28 scores is very wide (see Figure 1) and inferences cannot be made. Of particular note is the fact that 51.5% of all patients who have achieved the DAS28 CRP T2T LDAS or RDAS outcome (≤2.9) have a RAID score ≥2, in an unacceptable patient range. This represents a high proportion of LDAS and RDAS patients with unmet needs, and indicates there is much scope for investigation and improved intervention strategies for these patients who have achieved seemingly good DAS28 outcomes. The RAID has additional utility in this regard, as scrutiny of the seven domains identifies those areas scoring particularly poorly, enabling focussed interventions such as cognitive behavioural techniques. We found fatigue and sleep to be the most frequent high scoring domains in patients in DAS28-CRP R/LDAS but with a RAID ≥2. Fatigue is widely described to be a persisting long-term symptom in RA patients, including those in remission defined by DAS (7,9,19,20) and our data are consistent with this. However, many patients scored poorly on all of the 7 domains, indicating the need for a widespread package of care for truly holistic management. The high proportion of patients with a RAID score in the unacceptable range (≥2), yet in LDAS or RDAS, argues for a dual T2T strategy incorporating both an inflammation derived target and a PRO target to be holistic. This is in keeping with the conclusions of Ferreira et al (21) who advocate a 3 version composite score (SJC, TJC, CRP) as the target for immunosuppressive therapy and a separate disease impact target based on an expanded analysis of the patient global score, such as RAID. Our findings confirm that the RAID does function well as a T2T PRO, aiming for a score <2. The strength of our findings is that they demonstrate the utility of RAID in a real world routine care
setting. Nonetheless, the data are preliminary, as they are only from one center, and should be replicated in other settings and in larger numbers.

In summary we have found the RAID questionnaire to be simple and easy to incorporate into the routine care setting for patients with RA. The finding that >97% of all patients with a score in the patient acceptable range <2 are also in the DAS28-CRP categories of LDAS or RDAS provides potential time saving utility by avoiding face to face disease activity assessments for these patients. Conversely RAID reveals a high burden of unmet needs in patients in RDAS/LDAS, with over 50% scoring ≥2. Scrutiny of the seven domains assessed provides individualised opportunities for improved RA management, especially for fatigue and sleep problems. For truly holistic care there should be two T2T goals, one based on an inflammation derived measure and one on a PRO. The RAID performs well as a PRO in routine care.

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Figure Legends

Figure 1. The relation between DAS28-CRP and RAID scores.

Figure 2. Patients with DAS28-CRP \( \leq 2.9 \) (LDAS and RDAS) and RAID score \( \geq 2 \) (n=69).

Distribution (%) scoring each RAID domain mild (0-2), moderate (3-6), severe (7-10).
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## Supplementary Material

**Supplementary Table S1** Association of DAS28-CRP components with RAID using multiple mixed-effects linear regression

| Variable          | Coefficient | Standard Error | Significance Value | Lower Bound | Upper Bound | Standardised Coefficient |
|-------------------|-------------|----------------|--------------------|-------------|-------------|--------------------------|
| SJC (SQRT)        | -0.05       | 0.12           | 0.652              | -0.28       | 0.18        | -0.17                    |
| TJC (SQRT)        | 0.61        | 0.12           | **0.000**          | 0.37        | 0.85        | 0.23                     |
| PGA               | 0.06        | 0.01           | **0.000**          | 0.05        | 0.07        | 0.65                     |
| CRP (log)         | 0.18        | 0.09           | **0.048**          | 0.00        | 0.36        | 0.08                     |
| Age               | 0.01        | 0.01           | 0.414              | -0.01       | 0.02        | 0.03                     |
| Sex               | 0.36        | 0.25           | 0.157              | -0.14       | 0.85        | 0.05                     |
| Seropositive status | -0.19     | 0.28           | 0.509              | -0.74       | 0.37        | -0.03                    |

**Key**

Bold indicates statistical significance. SJC (SQRT): swollen joint count (square root transformed); TJC (SQRT): tender joint count (square root transformed); PGA: patient global assessment; CRP (log): C-reactive protein (log transformed).

**Supplementary figure legend**

**Supplementary Figure S1** Box and whisker plot showing mean (SD) RAID score in patients per DAS28-CRP disease activity category Patients categorized in DAS28-CRP remission (n=94), low (n=28), moderate (n=63) and high (n=13) disease activity

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