

ORIGINAL ARTICLE

Comparative analyses of responsiveness between the Rheumatoid Arthritis Impact of Disease score, other patient-reported outcomes and disease activity measures: secondary analyses from the ARCTIC study

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ABSTRACT

Objective To evaluate the responsiveness of the Rheumatoid Arthritis Impact of Disease (RAID) score compared with other patient-reported outcome measures (PROMs), inflammatory markers and clinical disease activity measures in patients with early rheumatoid arthritis (RA).

Methods Disease-modifying antirheumatic drug-naïve patients with RA with short disease duration were included in the treat-to-target ARCTIC trial and followed for 24 months. The responsiveness of the RAID score was evaluated using standardised response mean (SRM) and relative efficiency (RE) with respect to tender joints by Ritchie Articular Index (RAI). SRMs and REs were also calculated for other PROMs, inflammatory markers and clinical outcome measures. An SRM with value above 0.80 was considered high.

Results 230 patients with RA were included. The mean±SD symptom duration was 7.1±5.4 months and the baseline mean±SD RAID score was 4.49±2.14. At 3 months of follow-up, the mean±SD change score for RAID was -2.25±1.98 and the SRM (95% CI) -1.13 (-1.33 to -0.96). The RAID score showed high responsiveness both at 3 and 6 months (SRM≥0.80) and was more sensitive in detecting change than the reference, tender joints assessed by RAI.

Conclusions The RAID score proved to be highly responsive to change in patients with RA with short disease duration who followed a treat-to-target strategy. The RAID score was more efficient in detecting change than the reference (RAI) as well as most other PROMs.

INTRODUCTION

Patient-reported outcome measures (PROMs) provide valuable information about the impact of disease from a patient perspective and are considered as important as conventional disease activity and clinical outcome

Key messages

What is known about this subject?

- Responsiveness is an important quality in patient-reported outcome measures.
- Further validation of the responsiveness of the Rheumatoid Arthritis Impact of Disease (RAID) score has been suggested.

What does this study add?

- The RAID score showed high responsiveness to change compared with conventional disease activity measures and other patient-reported outcome measures.

How might this impact on clinical practice?

- The RAID score should be considered for use in clinical rheumatoid arthritis trials.

measures. They support patient-centred care and shared decision-making between patient and rheumatologist regarding treatment, in alignment with European League Against Rheumatism (EULAR) recommendations.¹⁻³

Efforts have been put into development and validation of rheumatoid arthritis (RA) PROMs in order to achieve valid outcomes.⁴⁻⁹ A prior EULAR initiative developed a patient-derived composite response index for RA for use in clinical trials, called the Rheumatoid Arthritis Impact of Disease (RAID) score.⁵ The RAID score includes the domains sleep disturbances, fatigue, coping and physical and emotional well-being, in addition to pain and physical disability, which are traditionally assessed. Further validation of the responsiveness of the RAID score has been suggested.^{6 10}

The objective of this study was to assess the changes in the RAID score in patients with early RA within the first 6 months of intensive disease-modifying antirheumatic drug (DMARD) treatment, and to evaluate the responsiveness of RAID after 3 and 6 months, compared with other PROMs and conventional disease activity measures.

METHODS

Patients and study design

This study used data from the ARCTIC trial (ClinicalTrials.gov identifier: NCT01205854).¹¹ All patients fulfilled the American College of Rheumatology (ACR)/EULAR classification criteria for RA, had symptom duration less than 2 years and were DMARD naïve. Patients were randomised 1:1 to a treat-to-target strategy with or without the use of ultrasound examination. All patients received treatment according to the same escalating DMARD treatment algorithm, in accordance with current EULAR treatment recommendations.^{2,11} Results from the ARCTIC trial showed no significant differences in clinical and radiographic outcomes between the two groups and both treatment groups were merged in the current analyses.

Assessments

Patients were assessed at 13 visits within 24 months. PROMs included the RAID score, the Patient-Reported Outcomes Measurement Information System 20-item Physical Function short form (PROMIS PF-20, range 20–100), the 36-item Short Form Health Survey (SF-36, 0–100) with calculations of physical and mental component summaries (PCS and MCS), fatigue Visual Analogue Scale (VAS, 0–100 mm) and joint pain VAS. Other assessments included swollen joint count (0–44), tender joint count (Ritchie Articular Index (RAI) with a graded (0–3) assessment of the tenderness of 26 joints (0–78)), erythrocyte sedimentation rate (ESR, mm/hour), C reactive protein (CRP, mg/L) and patient and physician global assessment of disease activity VAS. Disease Activity Score (DAS, 0–10) was also assessed, a four-variable composite score of 44-swollen joint count, RAI, ESR and patient global assessment.

The RAID score assesses the impact of disease on seven domains. Each RAID domain is measured on a simple numeric rating scale from 0 (best) to 10 (worst) and is assigned a weight in the sum score. Pain is weighted 21%, functional disability 16%, fatigue 15% and sleep disturbance, physical and emotional well-being as well as coping all 12%.^{5,6} An absolute and relative Minimal Clinically Important Improvement (MCII) of at least 3 points or more than 50% has been proposed, along with a Patient Acceptable Symptom State (PASS) of maximum 2.¹⁰ Suggested cut-off values for levels of impact of disease are RAID ≤3 (remission), RAID >3 and ≤4 (low impact of disease), RAID >4 and ≤6 (moderate impact of disease), and RAID >6 (high impact of disease).¹²

Statistical analyses

To evaluate the responsiveness of the different outcome measures, standardised response mean (SRM) was calculated as the ratio between the mean change score and the SD of the mean change score, expressed as $SRM = \frac{\text{mean change score}}{SD_{\text{change score}}}$ at 3 and 6 months of follow-up.¹³ Bootstrapping techniques (5000 replications) were applied to calculate the 95% CI of the SRMs. The threshold values for effect size suggested by Jacob Cohen were used to interpret the magnitude of the SRM and values above 0.20, 0.50 and 0.80 represent small, moderate and large responsiveness, respectively.¹⁴ The relative efficiencies (REs) with SE were calculated with respect to tender joints (RAI) at 3 months from baseline. RE equals the square of the ratio between the SRM of the outcome and the SRM of RAI and is given by the formula $RE = \left(\frac{SRM_1}{SRM_2}\right)^2$.^{15,16} An RE >1 suggests that a measure is more efficient in detecting change than the RAI.¹⁵ Tender joints, in this case by RAI, is an outcome measure which reflects inflammation and disease activity and based on these capacities it was selected as anchor for the RE analyses.

Baseline data were examined for floor effect, which can occur when more than 15% of the patients achieve the lowest possible score. The percentage of missing data was small and no imputation was performed.

Statistical analyses were performed using IBM SPSS Statistics V.24 and R V.3.0.2.

RESULTS

Baseline demographics, clinical characteristics and PROMs including the seven RAID domains from the 230 included patients are presented in [table 1](#). At baseline, the mean±SD DAS and RAID scores were 3.46±1.17 and 4.49±2.14, respectively, indicating a moderate disease activity in this cohort. One patient (0.4%) reported a RAID score of 0 at baseline. No floor effect was identified.

The mean change scores and SRM values of the outcome measures after 3 and 6 months are shown in [table 2](#). After 3 months, there was a marked treatment response in all measures, and the same tendency was observed at 6 months. The −1.95±1.09 points improvement in the DAS at 6 months led to a mean±SD DAS of 1.52±0.89, which indicates an average change from moderate disease activity to remission.^{11,17} The percentage of patients in DAS remission was 48 and 62 at 3 and 6 months of follow-up, equivalent of 99 and 131 patients, respectively.

The mean±SD change of the RAID score at 3 and 6 months was −2.25±1.98 and −2.39±1.98, respectively, which led to mean±SD scores of 2.28±1.84 and 2.08±1.78 at 3 and 6 months, respectively, which reflects that the group on average achieved a level of remission according to the suggested cut-off values. At 3 and 6 months, 34% and 40% of the patients had reached the suggested absolute MCII of 3 or more and 56% and 58% the relative MCII of 50% or more. Moreover, 53% and 56% of the patients reported a RAID score of 2 or less at 3 and 6 months, which is the suggested PASS.

Table 1 Baseline characteristics (values are mean±SDs unless stated otherwise)

Characteristics	N=230
Women N (%)	141 (61)
Anti-CCP positive N (%)	189 (82.2)
Age	51.4±13.7
Time since patient reported first swollen joint, months	7.1±5.40
RAID total	4.49±2.14
RAID pain	5.32±2.40
RAID functional disability	4.76±2.53
RAID fatigue	4.46±2.77
RAID sleep disturbance	3.90±3.08
RAID physical well-being	4.73±2.40
RAID emotional well-being	3.91±2.44
RAID coping	3.73±2.35
Disease Activity Score	3.46±1.17
Erythrocyte sedimentation rate	24.5±18.6
C reactive protein, median (IQR)	7.00 (3.00, 18.0)
Swollen joints*	10.5±7.51
Tender joints†	8.82±7.34
Patient global assessment VAS	49.8±24.4
Physician global assessment VAS	40.6±20.6
PROMIS physical function	39.08.5±8.68
Fatigue VAS	40.4±28.7
Joint pain VAS	47.8±24.1
SF-36 physical component summary	36.3±9.50
SF-36 mental component summary	49.1±10.6

Disease Activity Score (0–10), <1.6 (remission), ≥1.6–2.4 (low disease activity), >2.4–3.7 (moderate disease activity), >3.7 (high disease activity). Erythrocyte sedimentation rate (mm/hour, 1–140).

*Assessment of 44 joints (0–44).

†Ritchie Articular Index (0–78).

CCP, cyclic citrullinated peptide; PROMIS, Patient-Reported Outcome Information System (20–100); RAID, Rheumatoid Arthritis Impact of Disease (0–10); SF-36, 36-item Short Form Health Survey (0–100); VAS, Visual Analogue Scale (mm, 0–100).

DAS, RAID, RAI, PROMIS PF-20, joint pain, SF-36 PCS, physician and patient global assessment and swollen joint count all showed high responsiveness to change (SRM ≥0.80). ESR and CRP showed moderate responsiveness to change (SRM >0.5) while fatigue VAS and SF-36 MCS showed low responsiveness (SRM <0.5) (table 2).

The RE in relation to tender joints (RAI) after 3 and 6 months are illustrated in figure 1. DAS, physician global assessment and swollen joint count showed the highest efficiencies in detecting change. After 6 months, the RE of the RAID score increased slightly, which led to a slightly better performance than patient global assessment and joint pain VAS. The least efficient outcomes were ESR, CRP, fatigue VAS and SF-36 MCS.

DISCUSSION

Our study of patients with RA with short disease duration and followed by treat-to-target strategy found the RAID

score to be highly responsive to change and efficient in detecting change compared with several other PROMs.

At 3 and 6 months, more than half of the patients reported a RAID score of 2 or less, which is the suggested PASS and also indicates remission as proposed by Salaffi *et al.*¹² In comparison, 48% and 62% of the ARCTIC population achieved DAS remission at 3 and 6 months of follow-up.

More than half of the patients in the ARCTIC population achieved the suggested relative MCII of 50% or more after 3 months while a smaller proportion had an absolute improvement of 3 points or more. An absolute change of 3 points or more in an individual or a population with moderate disease activity level at baseline and short symptom duration, such as in the ARCTIC trial, might not be realistic to achieve.

The outcome with the highest relative sensitivity to change was DAS. Three of the DAS components, swollen joints, patient global assessment and joint pain, were

Table 2 Mean change±SD and standardised response mean (SRM) with 95% CIs for patient-reported outcomes and conventional disease activity measures from baseline to 3 months and from baseline to 6 months ordered by decreasing SRM at 3 months

	0–3 months		0–6 months	
	Change mean±SD	SRM (95% CI)	Change mean±SD	SRM (95% CI)
Disease Activity Score	−1.71±1.04	−1.63 (−1.89 to −1.42)	−1.95±1.09	−1.80 (−2.04 to −1.60)
Physician global assessment VAS	−26.2±19.2	−1.37 (−1.54 to −1.22)	29.2±20.7	−1.41 (−1.58 to −1.27)
Swollen joints*	−8.86±6.89	−1.28 (−1.46 to −1.14)	−9.63±7.41	−1.30 (−1.46 to −1.17)
Patient global assessment VAS	−28.3±24.2	−1.17 (−1.35 to −1.02)	−30.2±25.2	−1.20 (−1.38 to −1.05)
PROMIS physical function	9.14±7.91	1.16 (1.01 to 1.32)	9.98±8.48	1.18 (1.02 to 1.36)
Joint pain VAS	−27.7±24.4	−1.14 (−1.31 to −0.98)	−29.5±25.2	−1.17 (−1.35 to −1.02)
RAID	−2.25±1.98	−1.13 (−1.33 to −0.96)	−2.39±1.98	−1.21 (−1.38 to −1.06)
SF-36 physical component summary	8.99±9.02	1.00 (0.84 to 1.18)	9.19±9.47	0.97 (0.83 to 1.14)
Tender joints†	−5.75±6.03	−0.95 (−1.12 to −0.80)	−6.33±6.30	−1.01 (−1.15 to −0.88)
Erythrocyte sedimentation rate	−10.9±15.0	−0.73 (−0.83 to −0.63)	−11.7±16.5	−0.71 (−0.84 to −0.59)
C reactive protein	−9.68±18.4	−0.53 (−0.62 to −0.43)	−10.8±19.5	−0.55 (−0.63 to −0.48)
Fatigue VAS	−13.3±29.3	−0.45 (−0.60 to −0.32)	−16.0±29.8	−0.54 (−0.68 to −0.40)
SF-36 mental component summary	3.89±10.6	0.37 (0.23 to 0.52)	3.02±10.8	0.28 (0.15 to 0.43)

*Assessment of 44 joints (0–44).

†Ritchie Articular Index (0–78).

RAID, Rheumatoid Arthritis Impact of Disease (0–10); VAS, Visual Analogue Scale (mm, 0–100); PROMIS, Patient-Reported Outcome Information System (20–100); SF-36, 36-item Short Form Health Survey (0–100).

highly responsive as single domains. The outcomes with the highest relative responsiveness all reflect physical aspects of the disease, whereas the RAID score includes emotional well-being and coping and still seems to show a high efficiency in detecting change.

Patient global assessment (PGA) and RAID are both global patient-reported indexes and both measures are equally responsive to change, according to this study. PGA is already incorporated in the EULAR/ACR core set of outcome measures for RA. The question whether the RAID score could replace the patient global assessment has been raised.⁶ Some considerations in this regard would be that the PGA is less time consuming to perform compared with the RAID score. If a global assessment with no differentiation is satisfying, then the PGA should be sufficient. However, RAID provides more specific details about the impact of disease.

The data imply that the RAID score was more efficient in detecting change than the other multidimensional PROMs, SF-36 PCS and MCS and PROMIS physical function after 6 months. Compared with these outcomes, the RAID score separates itself in the sense that it incorporates the traditional health-related domains as well as sleep, fatigue, well-being and coping that patients with RA perceive as important.^{18–20} Furthermore, the RAID score distinguishes itself as a disease-specific outcome compared with the generic SF-36 and PROMIS physical function.

For an outcome to be able to detect treatment effect or any change over time, it needs to be responsive. There

are a variety of statistical approaches to measuring responsiveness and there is no consensus yet about which approach is the best.^{16 21 22} Measuring the magnitude of change detected by an instrument is one approach and multiple effect size indices are applied for this purpose. There is some evidence to suggest that using the SD of the change score (SRM) rather than the SD of the baseline score (ES) is more informative because it includes the variety of the change scores,¹³ which is why we chose to use SRM and not ES. It was as well a factor that SRM had been used to measure the responsiveness in the finalisation and validation study of the RAID score and we wanted to be able to compare the results.

In conclusion, this early RA intervention study provides support for the responsiveness of the RAID score. According to the EULAR/ACR recommendations for reporting results in clinical trials, assessing changes is important.²³ The changes in the RAID score corresponded well with the changes in the DAS with regard to the proportion of patients in remission after 6 months. The RAID score was more efficient in detecting change than the reference (RAI) as well as other PROMs. The RAID score is a highly responsive patient-reported composite index which, with the suggested cut-off values, MCII and PASS should be considered for intervention studies in patients with RA. Further research should assess the responsiveness to change of the RAID score regarding the performance in RA flares.

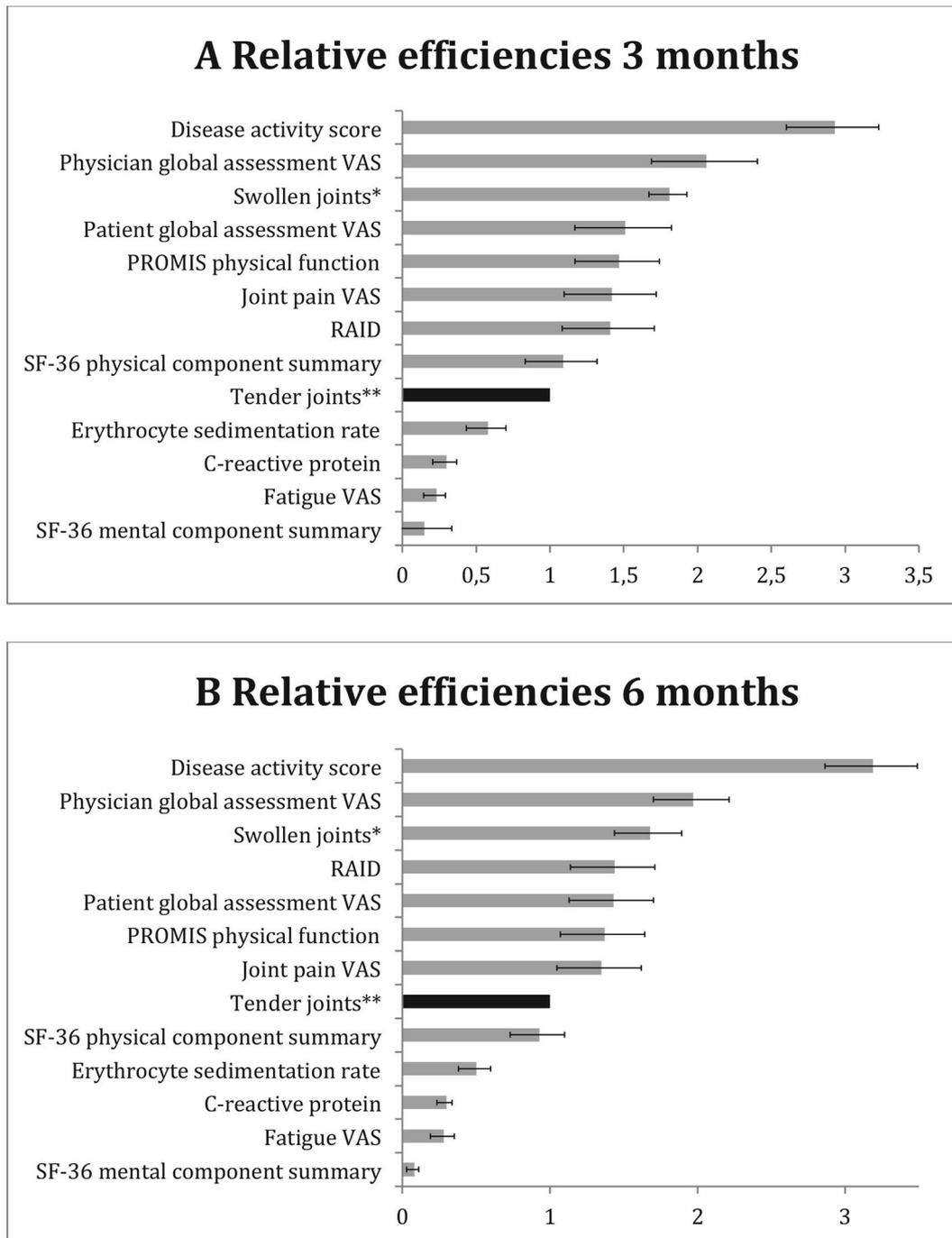


Figure 1 Relative efficiencies to tender joints (Ritchie Articular Index, RAI) of the various outcomes reflecting disease activity after 3 months (A) and 6 months (B) of follow-up (tender joints (RAI)=reference with a relative efficiency of 1.00). PROMIS, Patient-Reported Outcome Information System; RAID, Rheumatoid Arthritis Impact of Disease; SF-36, 36-item Short Form Health Survey; VAS, Visual Analogue Scale. *Assessment of 44 joints. **Ritchie Articular Index.

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Contributors KH designed the current study, analysed and interpreted data, and wrote the report. JS analysed and interpreted data, and reviewed the manuscript. TKK designed the ARCTIC study, contributed to the current study design, interpreted data and reviewed the manuscript. A-BA and EAH designed the current study and the ARCTIC study, recruited and enrolled participants, collected, analysed

and interpreted data, and reviewed the manuscript. All authors have approved the final draft and vouch for the accuracy and completeness of the data and analyses.

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