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ORIGINAL RESEARCH

Agreement between patient-reported flares and clinically significant flare status in patients with rheumatoid arthritis in sustained remission: data from the ARCTIC REWIND trials

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ABSTRACT

Objectives To explore the agreement between patient-reported flare status and clinically significant flare status in patients with rheumatoid arthritis (RA) in sustained remission.

Method Patients with RA in remission for ≥12 months on stable treatment were included in the ARCTIC REWIND tapering trials and pooled 12-month data used in current analyses. Patient-reported flare status was assessed according to the Outcome Measures in Rheumatology flare questionnaire; 'Are you having a flare of your RA at this time?' (yes/no). A clinically significant flare was defined as a combination of Disease Activity Score (DAS) >1.6, increase in DAS of ≥0.6 and 2 swollen joints, or the rheumatologist and patient agreed that a clinically significant flare had occurred. Agreement coefficient, sensitivity, specificity and predictive values of patient-reported flare status with regard to clinically significant flare status were determined.

Results Of 248 patients, 64% were women, age 56.1 (11.8) years, disease duration 4.1 (2.8–7.4) years, DAS 0.8 (0.3). 35% of patients reported a flare at least once, clinically significant flares were recorded in 21%. 48/53 clinically significant flares (91%) led to an intensification of disease-modifying antirheumatic drugss. In 621/682 (91%) visits, patient-reported and clinically significant flare status were in agreement, agreement coefficient 0.89. Sensitivity and specificity were both 91%, positive predictive value of patient-reported flare status 46% and negative predictive value 99%.

Conclusion Among patients in sustained remission, patient-reported flare status was accurate in ruling out a clinically significant flare. About half of the patient-reported flares were assessed to be clinically significant. These findings support a potential for using patient-reported flare status in remote monitoring of patients with RA in sustained remission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patient-reported outcomes such as the Rheumatoid Arthritis Flare Questionnaire could contribute to detection of disease activity flares in regular clinical practice and in remote monitoring.

⇒ Further knowledge is needed on the associations between patient-reported flare status and clinical flare status.

WHAT THIS STUDY ADDS

⇒ The overall agreement between patient-reported flare status and clinically significant flare status in patients with RA who had achieved sustained remission was strong. Patient-reported flare status showed high sensitivity to flare and was accurate in ruling out a flare. Almost one in two patient-reported flares were assessed to be clinically significant.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may support the use of patient-reported flare assessment as a safe and accurate way to detect and rule out clinically significant flares.

INTRODUCTION

Sustained remission has become an achievable goal for a large proportion of patients with rheumatoid arthritis (RA).[1–3] However, disease activity flares can occur even after prolonged periods in remission and are associated with poor clinical outcomes, radiographic progression, functional impairment and increased cardiovascular risk.[4–8] Detection of disease activity flares is important for the patient to receive timely clinical evaluation and potential adjustment of treatment to regain control of the disease.

A standardised definition of RA flare does not yet exist, but according to the 2008 Outcome Measures in Rheumatology (OMERACT) definition, a flare is a 'cluster of symptoms of sufficient duration and intensity that cannot be self-managed by the patient and require initiation, change or increase in therapy'.[9] The concept of flare is challenging to define, as the perception of flare may differ between patients and healthcare providers. Patients tend to consider subjective symptoms such as pain, reduced mobility, sleep and emotional well-being more important than clinical disease activity outcomes.[10 11] As a result, a core domain set to assess RA flare and the OMERACT RA Flare Questionnaire (RA-FQ) was developed as a patient-reported outcome to monitor disease activity and detect flares, incorporating both patients' and health professionals' perspectives.[12–14] Other questionnaires have also been developed to assess flares in this population.[15 16]

Patient-reported outcome measures such as the RA-FQ could contribute to the detection of disease activity flares in regular clinical settings and in remote monitoring of patients with RA in stable remission.[17 18] The objective of the current study was to examine the agreement between patient-reported flares and clinically significant flares in disease activity in patients with RA in sustained remission.

METHOD

Study design and patients

We used data from the two open-label, randomised ARCTIC REWIND trials (clinicalTrials.gov ID: NCT01881308) assessing the effect of tapering of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and tumour necrosis factor inhibitors (TNFi) in patients with RA in sustained remission.[19 20] Patients (18–80 years) were eligible if they fulfilled the American College of Rheumatology/European Alliance of Associations for Rheumatology 2010 classification criteria for RA, had been in sustained remission for at least 12 months on stable medication with Disease Activity Score (DAS) <1.6 and no swollen joints at inclusion (of 44 assessed).[21] For the current analyses, data from the first 12 months of the two trials were combined, and patients who initiated therapy were included in analyses. Patients in the csDMARD trial were randomised 1:1 to stable or half dose treatment for the first year. In the TNFi trial, patients were randomised 1:1 to continued stable TNFi treatment or to tapering and discontinuation of TNFi with stable csDMARD comedication. Study visits were conducted every 4 months, and if a flare was suspected between visits the patient should be seen within a week. If a flare was recorded, the full dose of the patient's medication was reinstated in the tapering groups, while in the stable groups, treatment was adjusted according to current recommendations.

Patient and public involvement

Patient representatives were involved in the development of research questions and interpretation of the results.

Assessments

Information about age, sex, body mass index (BMI), educational level (dichotomised in up to 12 years or more than 12 years of education), time since first swollen joint, presence of rheumatoid factor (RF), anticitrullinated peptide antibodies (ACPA) and comorbidities were established at baseline. Number of comorbidities was dichotomised as either none or one or more, and frequencies of osteoarthritis, fibromyalgia and depression were assessed.

Clinical, laboratory and ultrasound assessments

Clinical characteristics recorded at baseline and at each study visit included the composite disease activity measures; DAS, DAS based on 28 joints (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) as well as swollen joints (of 44 joints assessed), tender joints assessed by Ritchie Articular Index (RAI), physician global assessment (PhGA) of disease activity on a visual analogue scale (VAS, 0–100) and laboratory assessments of inflammation by erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).[22–25] Ultrasound assessments of 32 joints were performed at baseline, 12 months and if a clinically significant flare was identified, with scoring of grey scale and power Doppler with semiquantitative scores from 0 to 3 using an atlas for reference.[26] Higher scores indicated higher disease activity for all disease activity measures.

Patient-reported outcome measures

Patient-reported outcome measures at each study visit included patient global assessment of disease activity (PGA), fatigue and joint pain (VAS, 0–100) during the last week, the Rheumatoid Arthritis Impact of Disease (RAID) total score and individual components completed on numeric rating scales (NRS, 0–10) and Patient-Reported Outcome Information System (PROMIS) physical function (range 20–100, translated to a T score with a mean of 50 and an SD of 10).[27 28] Higher scores indicated poorer outcomes for all patient-reported outcome measures except PROMIS where lower scores implied poorer outcome. All questionnaires were to be completed at the study visit before the clinical evaluation.

Assessment of flare

A clinically significant flare in disease activity was defined as a combination of DAS >1.6 (loss of remission), an increase in DAS ≥0.6 (larger than minimal detectable change)[29] and at least two swollen joints of 44 examined (clinically active arthritis), or, if these criteria were not fulfilled, a flare could be recorded if the patient and the rheumatologist agreed that a clinically significant flare had occurred.[19 20]

Patient-reported flare status, duration and severity of the flare, as well as self-management strategies, were assessed using the OMERACT preliminary FLARE questionnaire V.2.1 at all study visits except the baseline visit (online supplemental material). The question regarding

patient-reported flare status was phrased 'Are you having a flare of your RA at this time?' (yes/no) identical with the phrasing in the current OMERACT RA-FQ.[12 30]

Patients who reported to have a flare, rated the severity of the flare during the last week on a NRS from 0 to 10 with higher scores indicating higher severity of symptoms, and reported the duration of the flare with the response options 1–3, 4–7, 8–14 and >14 days. Furthermore, they were asked to complete a section of the questionnaire regarding self-management strategies and were allowed to choose as many strategies as applied in relation to their flare. Self-management strategies included not doing anything different, reducing the amount of activities and/or rest more, avoiding planned activities, non-pharmacologic management (massage, heat/cold packs, exercise), taking more painkillers, taking more steroids and asking for help from rheumatologist. In accordance with the study protocol, patients were asked not to self-administer steroids even though it was listed as an option.

Statistical analyses

Baseline characteristics were summarised using frequencies (percentages), mean (SD) or median (IQR) as appropriate. Data from all visits up to and including a patients first clinically significant flare were included in the analyses, and visits after the first clinically significant flare were censored. The performance of patient-reported flare status with regard to clinically significant flare status (reference standard) was assessed by estimating the percentage agreement and agreement coefficient (AC_1), sensitivity, specificity, predictive values and likelihood ratios using bootstrapping techniques to account for repeated measures, as patients could report a flare multiple times, whereas only the first clinically significant flare (if any) of each patient was included in our analyses.[31–34] Sensitivity analyses were performed on flares that led to an intensification of DMARD therapy.

Separate mixed effects linear regression models with patient as a random effect were performed to explore differences in clinical, laboratory, ultrasound and patient-reported outcomes in the two patient-reported flare states (yes/no). The models were adjusted for baseline values of the explanatory variable and time was included as a categorical variable based on the successive study visits. Likewise, differences in clinical, laboratory, ultrasound and patient-reported outcomes were explored in patient-reported flares, which corresponded with a clinically significant flare at the same visit versus patient-reported flares not confirmed as a clinically significant flare at the same visit.

We hypothesised that a patient-reported flare not confirmed as a clinically significant flare at the same visit could indicate a worsening in disease activity and assessed the change in clinical and patient-reported outcomes between the visit prior to and the visit of the first patient-reported flare using paired t-test and Wilcoxon signed-rank test in these cases. In addition, we assessed how many of these patient-reported flares were followed by a clinically significant flare at the subsequent visit and within the first 12 months of the study.

Visits where either patient-reported flare status or clinically significant flare status was missing were excluded from the analyses. Missing RAID items were imputed according to the formal scoring rules and calculation rules. No additional imputation of data was performed. All 95% CIs and p values were based on two-sided hypothesis tests, where a p value of <0.05 was considered statistically significant. All analyses were executed in Stata V.16.0 (StataCorp).

RESULTS

Two hundred and forty-eight patients were included in the analyses, 159 (64%) were women, median (IQR) disease duration was 4.1 (2.8–7.4) years and mean (SD) age 56.1 (11.8) (table 1). At baseline, mean (SD) DAS was 0.8 (0.3) and median (IQR) PGA VAS 3.0 (1.0–11.0). Data on both patient-reported flare status and clinically significant flare status were available at 682 out of 703 visits, thus 21 visits (3%) were excluded from the analyses (see figure 1).

Patient-reported flares

During the 682 visits, there were 104 patient-reported flares with 88 of 248 (35%) patients reporting at least one flare. Of these 88 patients, 75 (85%) reported a flare one time, 11 (13%) reported a flare two times, while two patients (2%) reported more than two flares. Median (IQR) severity of patient-reported flares was 3.0 (2.0–5.0) on a scale from 0 to 10 and the majority of flares, 61/104 (60%), were reported to last more than 14 days. Of the 104 patient-reported flares, 75 (72%) were reported during prescheduled visits, whereas 29/104 (28%) were reported at unscheduled visits conducted in relation to suspected flares.

Agreement between patient-reported flare status and clinically significant flare status

Fifty-three of 248 patients (21%) experienced a clinically significant flare during the 12 months of follow-up (figure 1), and clinically significant flares were registered at 53/682 (8%) of the visits (figures 1 and 2). The percentage agreement of patient-reported and clinically significant flare status was 91% (621 of 682 visits). Agreement coefficient (AC_1) (95% CI) was 0.89 (0.86 to 0.92) corresponding to almost perfect agreement according to Landis and Koch's benchmark criteria.[35] The sensitivity (95% CI) of patient-reported flare with regard to clinically significant flare was 91% (83 to 98), with a specificity of 91% (89 to 94). The positive likelihood ratio (95% CI) was 10.2 (6.8 to 13.5), negative likelihood ratio was 0.1 (0.03 to 0.2), with positive predictive value (95% CI) 46% (37 to 56) and negative predictive value 99% (98 to 100).

Of 53 clinically significant flares recorded, 48 flares (91%) led to an intensification of DMARD therapy in agreement with the trial protocol.[19 20] There was no significant difference in the proportion of DMARD

Table 1 Baseline characteristics

Female (%)	159 (64)
Age, years	56.1 (11.8)
Educational level>12 years	151 (61)
Time since first swollen joint, years	4.1 (2.8–7.4)
Type of DMARD*	
csDMARD†	156 (63)
TNFi‡	92 (37)
BMI§	26.1 (4.2)
Stable treatment	123 (49.6)
Tapered treatment	125 (50.4)
Comorbidities≥1	185 (75)
Depression	8 (3)
Fibromyalgia	0 (0)
Osteoarthritis	50 (20)
RF¶ positive (IgM or IgA)	167 (67)
Anti-CCP** positive	191 (77)
Disease Activity Score, DAS (0–10) g	0.8 (0.3)
DAS28††	1.6 (0.6)
SDAI‡‡	0.8 (0.4–1.9)
CDAI§§	0.5 (0.2–1.5)
Swollen joint count (0–44)¶¶	0.0 (0.0–0.0)
Tender joints, Ritchie Articular Index (0–78)***	0.0 (0.0–0.0)
Erythrocyte sedimentation rate	7.0 (4.0–14.0)
C-reactive protein mg/L	2.0 (1.0–3.0)
Ultrasound PD score†††	0.0 (0.0–0.0)
Ultrasound GS score†††	1.0 (0.0–3.0)
Physician global assessment VAS (0–100 mm)	0.0 (0.0–3.0)
Patient global assessment VAS (0–100 mm)	3.0 (1.0–11.0)
RAID total score NRS (0–10)‡‡‡	0.6 (0.1–1.4)
Pain	1.0 (0.0–2.0)
Functional disability	0.0 (0.0–1.0)
Fatigue	1.0 (0.0–2.0)
Sleep	0.0 (0.0–1.0)
Physical well-being	1.0 (0.0–2.0)
Emotional well-being	0.0 (0.0–1.0)
Coping	0.0 (0.0–1.0)
PROMIS physical function§§§	54.4 (48.2–62.5)
Joint pain VAS¶¶¶ (0–100 mm)	3.0 (1.0–10.0)
Fatigue VAS¶¶¶ (0–100 mm)	7.0 (1.0–25.0)

Values are expressed in mean (SD), median (IQR) and proportion (percentage) as appropriate. N=248.
*Disease modifying anti-rheumatic drug.
†Tumour necrosis factor inhibitor.
‡Conventional synthetic.
§Body mass index.
¶Rheumatoid factor.
**Cyclic citrullinated peptide.
††Disease Activity Score (DAS) includes a swollen joint count of 44 joints, assessment of tender joints by Ritchie Articular Index (RAI), erythrocyte sedimentation rate (ESR) and a patient global assessment of the disease activity from 0 to 100 mm on a visual analogue scale. DAS remission<1.6, DAS low disease activity 1.6–2.4, DAS moderate disease activity 2.4–3.7, DAS high disease activity>3.7.
¶¶Clinical Disease Activity Index.
***Swollen joint count is the number of swollen joints in an assessment of 44 joints.
†††Ritchie Articular Index (RAI) is a graded assessment of tenderness (0–3) of 26 joint regions with a sum score ranging from 0 to 78 where higher scores indicate more tenderness.
‡‡‡Ultrasound assessment of synovitis by synovial vascularity using power Doppler (PD) and morphology and quantity with grey scale (GS). The ultrasound examination was performed using 0–3 semiquantitative scoring systems for both GS and PD in 32 joints.
§§§Rheumatoid Arthritis Impact of Disease.
¶¶¶PROMIS: Patient Reported Outcome Information System, range 20–100, translated into a T-score with a mean of 50 and an SD of 10.[28]
****Related to rheumatoid arthritis the last week.
BMI, body mass index; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drugs; NRS, numeric rating scale; PROMIS, Patient-Reported Outcome Information System; RAID, Rheumatoid Arthritis Impact of Disease; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; TNF, tumour necrosis factor; VAS, visual analogue scale.

escalations in flares based on DAS criteria and flares based on consensus between the patient and rheumatologist. The remaining 5/53 flares were treated with short-term oral glucocorticoids, intra-articular injections and non-steroidal anti-inflammatory drugs (NSAIDs). Sensitivity analyses showed similar agreement between patient-reported flare status and flare leading to intensification of DMARD therapy as when using the reference standard for flare (online supplemental table 2).

Disease activity in patient-reported flares

Patients reporting a flare had significantly higher swollen joint count, with adjusted difference (95% CI) 1.3 (1.1 to 1.5) compared with patients not reporting a flare. Similar results were observed for CRP, with adjusted difference (95% CI) 4.8 (3.6 to 5.9), ESR (adjusted difference 95% CI 5.7 (4.3 to 7.0)) and ultrasound power Doppler score (adjusted difference 95% CI 0.7 (0.3 to 1.1)), all p values <0.001 (table 2). PGA VAS was 23.0 mm (95% CI 20.2 to 25.9) higher in patients who reported a flare, and patient-reported flare was associated with a statistically significant increase in all RAID components, with the largest increase observed in pain, physical function and physical well-being (table 2).

Patients who reported a flare and had a clinically significant flare at the same visit reported more severe flares and had significantly higher disease activity by clinical, laboratory, ultrasound and patient-reported outcomes compared with patients who reported a flare, which did not coincide with a clinically significant flare at the same visit (online supplemental table 3).

Fifty six of 104 (54%) patient-reported flares did not concur with a clinically significant flare at the same visit (figures 1 and 2). We observed a small but statistically significant overall increases in DAS, swollen joint count,

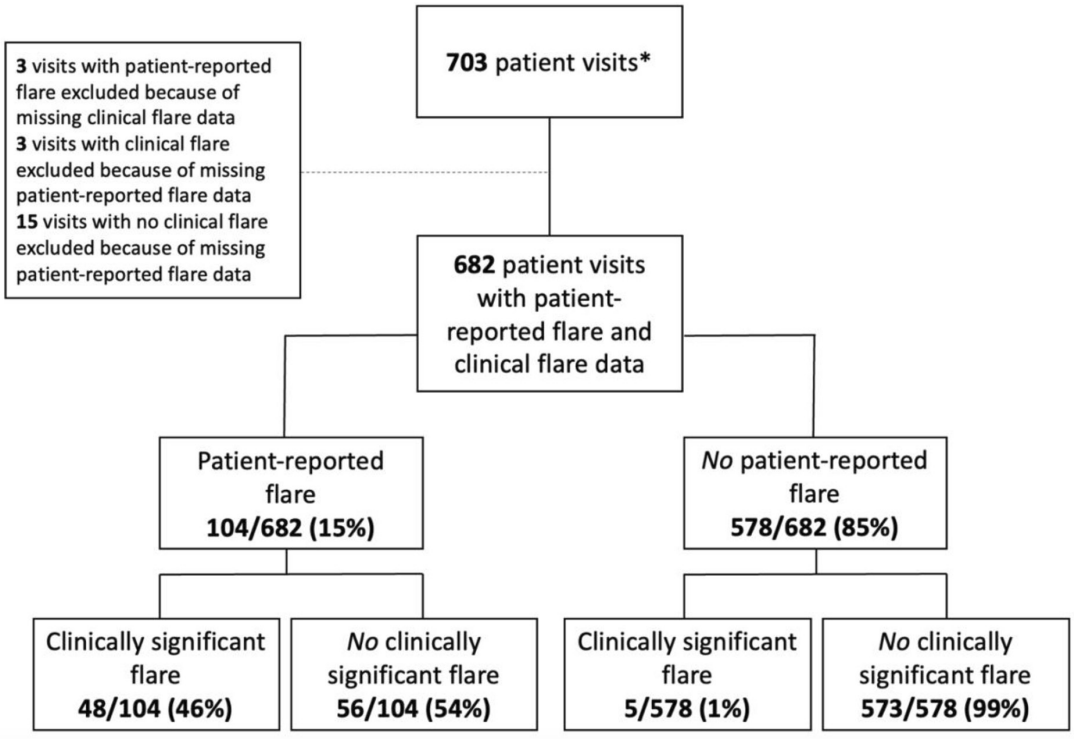

Figure 1 Flowchart showing patient visits with patient-reported flare and clinical flare data available. Distribution of patient-reported flare (yes/no) and clinically significant flare (yes/no) at visits up until the first (if any) clinically significant flare during the 12 months follow-up for the 248 patients included in the current analyses. *Including all visits except baseline visits where patients were required to be in DAS remission with no swollen joints according to inclusion criteria. Patient-reported flare status was not assessed at baseline. DAS, Disease Activity Score.

ESR and PhGA from the previous visit to the first patient-reported flare visit in those patients (table 3). Furthermore, 5 (9%) of these 56 patient-reported flares were followed by a clinically significant flare at the subsequent visit, while in additional 8 (14%), a clinically significant flare occurred at a later visit during the 12 months follow-up. Ten patient-reported flares were reported on the 12-month visit, thus data regarding clinically significant flare status at the next visit were not available for analyses.

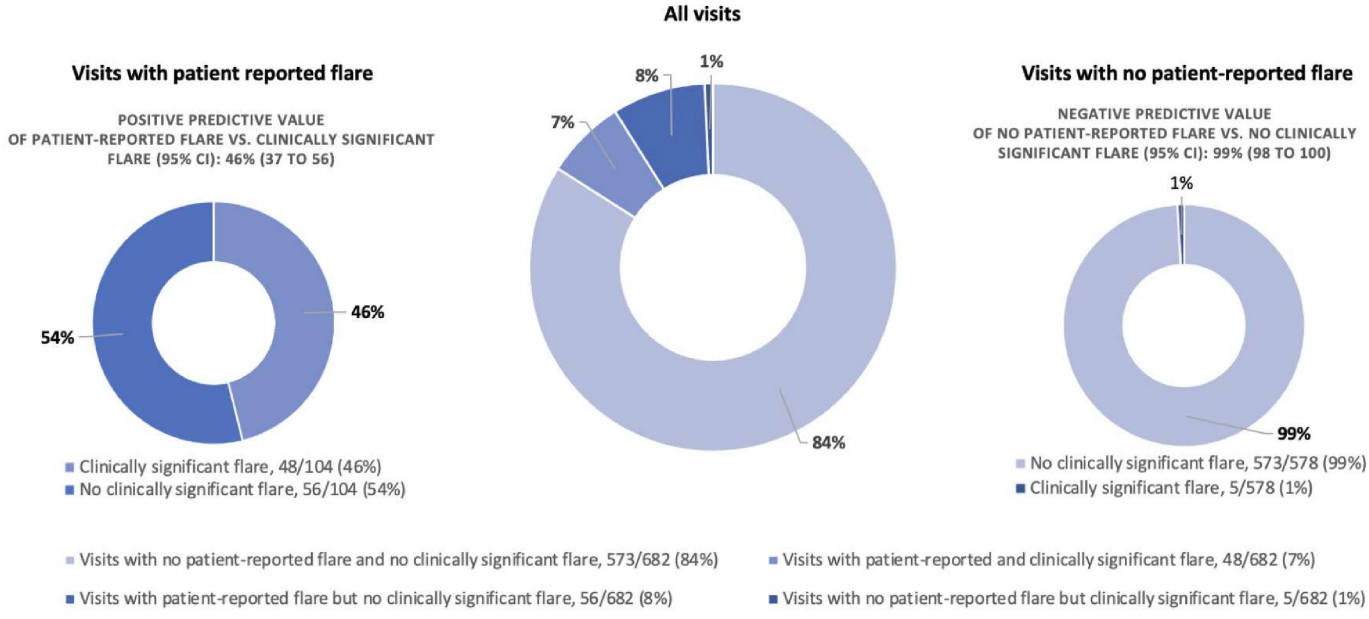

Figure 2 Distribution of patient-reported flare status and clinically significant flare status across patient visits, positive predictive value and negative predictive value of patient-reported flare status with regard to clinically significant flare status.

Table 2 Comparison of outcomes in patient-reported flares versus no patient-reported flare

Outcome	Visits where patients did not report a flare (n=578)	Visits where patients reported a flare (n=104)	Adjusted difference* (95% CI)	P value
DAS†	0.9 (0.4)	1.7 (0.8)	0.8 (0.7 to 0.9)	< 0.001
DAS28‡	1.7 (0.7)	2.8 (1.2)	1.2 (1.0 to 1.3)	< 0.001
SDAI§	1.0 (0.5–2.3)	7.0 (3.7–11.8)	6.5 (5.8 to 7.2)	< 0.001
CDAI¶	0.7 (0.2–2.0)	6.7 (3.4–10.8)	6.0 (5.3 to 6.6)	< 0.001
Swollen joint count†	0.0 (0.0–0.0)	1.0 (0.0–2.0)	1.3 (1.1 to 1.5)	< 0.001
Tender joints**	0.0 (0.0–0.0)	1.0 (0.0–3.0)	1.5 (1.3 to 1.7)	< 0.001
ESR†	8.0 (4.0–14.0)	11.0 (6.0–20.0)	5.7 (4.3 to 7.0)	< 0.001
CRP††	2.0 (1.0–3.0)	3.5 (1.0–9.0)	4.8 (3.6 to 5.9)	< 0.001
Ultrasound PD score‡‡	0.0 (0.0–0.0)	0.0 (0.0–2.0)	0.7 (0.3 to 1.1)	< 0.001
Ultrasound GS score‡‡	1.0 (0.0–3.0)	3.0 (1.0–6.0)	1.7 (0.6 to 2.8)	0.003
PhGA VAS§§,‡‡‡	1.0 (0.0–5.0)	14.0 (5.0–22.0)	11.0 (9.5 to 12.5)	< 0.001
PGA VAS¶¶,†,‡‡‡	4.5 (1.0–12.0)	30.5 (13.5–50.5)	23.0 (20.2 to 25.9)	< 0.001
RAID***,‡‡‡ total score	0.6 (0.1–1.4)	1.9 (1.0–3.9)	1.4 (1.2 to 1.7)	< 0.001
Pain	1.0 (0.0–2.0)	3.0 (2.0–5.5)	2.4 (2.1 to 2.7)	< 0.001
Functional disability	0.0 (0.0–1.0)	2.0 (1.0–5.0)	1.7 (1.4 to 1.9)	< 0.001
Fatigue	1.0 (0.0–2.0)	2.0 (0.0–4.0)	1.0 (0.7 to 1.3)	< 0.001
Sleep	0.0 (0.0–1.0)	1.0 (0.0–3.0)	1.2 (0.9 to 1.5)	< 0.001
Physical well-being	1.0 (0.0–2.0)	2.0 (1.0–4.0)	1.6 (1.3 to 1.9)	< 0.001
Emotional well-being	1.0 (0.0–1.0)	1.0 (0.0–3.0)	1.0 (0.7 to 1.2)	< 0.001
Coping	0.0 (0.0–1.0)	1.0 (0.0–3.0)	1.3 (1.0 to 1.6)	< 0.001
PROMIS physical function†††	54.4 (48.2–62.5)	47.4 (42.9–54.4)	–5.2 (-6.2 to 4.2)	< 0.001
Joint pain VAS‡‡‡	4.0 (1.0–12.0)	31.0 (13.0–50.5)	22.5 (19.7 to 25.3)	< 0.001
Fatigue VAS‡‡‡	6.0 (1.0–26.0)	14.5 (4.0–39.5)	5.6 (2.4 to 8.9)	0.001

Values are expressed in means (SD) or medians (IQR) and adjusted difference (95% CI) with corresponding p values. Results are based on linear mixed models for each outcome variable with patient-reported flare (yes/no) as explanatory variable. Analyses were based on 682 visits.
*Analyses were adjusted for baseline scores, repeated measures from the same individual and time was included as a categorical variable based on the successive study visits.
†Disease Activity Score includes a swollen joint count of 44 joints, assessment of tender joints by Ritchie Articular Index, erythrocyte sedimentation rate (ESR) and a patient global assessment of the disease activity from 0 to 100 mm on a visual analogue scale (VAS). DAS remission<1.6, DAS low disease activity 1.6–2.4, DAS moderate disease activity 2.4–3.7, DAS high disease activity>3.7.
‡Disease activity score based on evaluation of 28 joints.
§Simplified Disease Activity Index.
¶Clinical Disease Activity Index.
**Ritchie Articular Index (RAI) is a graded assessment of tenderness (0–3) of 26 joint regions with a sum score ranging from 0 to 78 where higher scores indicate more tenderness.
†† C-Reactive Protein.
‡‡Ultrasound assessment of synovitis by synovial vascularity using power Doppler (PD) and morphology and quantity with grey scale (GS). The ultrasound examination was performed using 0–3 semiquantitative scoring systems for both GS and PD in 32 joints.
§§Physician Global Assessment of disease activity.
¶¶Patient global assessment of disease activity
***Rheumatoid Arthritis Impact of Disease.
†††PROMIS: Patient Reported Outcome Information System, range 20–100, translated into a T-score with a mean of 50 and an SD of 10.[28]
‡‡‡Related to rheumatoid arthritis the last week.
CDAI, Clinical Disease Activity Index; CRP, C reactive protein; PGA, patient global assessment of disease activity; PhGA, physician global assessment; RAID, Rheumatoid Arthritis Impact of Disease; SDAI, Simplified Disease Activity Index.

Self-management strategies

The two most commonly used self-management strategies during patient-reported flares were to take more painkillers (recorded 50 times) and not to do anything different (recorded 45 times). A reduction of activities was registered 28 times and 25 times patients reported to have asked the rheumatologist for help. Less frequent strategies were avoiding planned activities (reported

Table 3 Change in clinical and patient-reported outcomes from the last visit prior, to the visit of the first patient-reported flare not verified as a clinically significant flare

Outcome	Last visit prior to first patient-reported flare without clinically significant flare	First patient-reported flare visit without clinically significant flare	Mean (SD) change between visits, P values*
DAS	0.8 (0.4) 0.8 (0.5–1.0)	1.3 (0.6) 1.3 (0.8–1.7)	0.5 (0.5) <0.001
Swollen joint count	0.0 (0.2) 0.0 (0.0–0.0)	0.3 (0.6) 0.0 (0.0–0.1)	0.3 (0.6) 0.005
Tender joint count	0.3 (0.6) 0.0 (0.0–0.0)	1.2 (1.5) 1.0 (0.0–2.0)	1.0 (1.5) <0.001
ESR	8.9 (7.2) 7.0 (3.0–11.5)	11.9 (10.8) 8.0 (4.0–14.0)	3.1 (7.4) 0.005
CRP	2.1 (2.1) 1.0 (1.0–2.0)	3.9 (4.4) 2.0 (1.0–5.0)	1.8 (3.9) 0.0035
PGA	10.7 (14.2) 4.0 (1.0–18.0)	23.6 (19.2) 19.0 (8.0–38.0)	13.4 (14.5) <0.001
PhGA	3.8 (5.2) 2.0 (0.0–5.0)	10.1 (10.0) 7.0 (4.0–15.0)	6.4 (10.9) <0.001
RAID pain	1.4 (1.4) 1.0 (0.0–2.0)	3.1 (2.1) 3.0 (1.0–4.0)	1.8 (2.0) <0.001
RAID physical disability	0.9 (1.3) 0.0 (0.0–1.0)	1.9 (2.2) 1.0 (0.0–3.0)	1.0 (1.9) <0.001

Mean (SD) and median (IQR) at each visit, mean change (95% CI). Paired t-test and Wilcoxon signed-rank test. Analyses were based on 48 visits.
DAS: Disease Activity Score includes a swollen joint count of 44 joints, assessment of tender joints by Ritchie Articular Index, erythrocyte sedimentation rate (ESR) and a patient global assessment of the disease activity from 0 to 100 mm on a visual analogue scale. Swollen joint count: 44 joints examined. Tender joint count: assessment of tender joints by Ritchie Articular Index which is a graded assessment of tenderness (0–3) of 26 joint regions with a sum score ranging from 0 to 78 where higher scores indicate more tenderness. PGA: Patient Global Assessment of disease Activity on a visual analogue scale from 0 to 100 mm. PhGA: Physician Assessment of Disease Activity on a visual analogue scale from 0 to 100 mm. RAID: Rheumatoid Arthritis Impact of Disease, range 0–10 on a numeric rating scale.
*P values were similar for Wilcoxon signed-rank test and paired t-test.
CRP, C reactive protein.

13 times), non-pharmacologic management such as massage, heat/cold packs, exercise (reported 10 times) and to take steroid tablets (reported three times).

DISCUSSION

Among patients with RA who had achieved sustained remission, we found a strong agreement between patient-reported flare status and clinically significant flare status. Flare reported by the patient was sensitive for detection of clinically significant flares, and nearly one in two patient-reported flares were verified as clinically significant flares. If the patient did not report a flare, there was a 99% probability that he or she did not have a clinically significant flare.

Frequent remote monitoring with patient-reported outcome measures such as the RA-FQ could improve outcomes by facilitating early detection of flare.[17 18 36 37] For patients in sustained remission, remote monitoring could potentially replace some clinical visits and contribute to more efficient use of healthcare resources. In our study, the patient-reported flare status corresponded well with clinically significant flare status, with high percentage agreement and agreement coefficient. However, previous studies indicate that agreement tends to be lower among patients in low, moderate and high disease activity than in patients in remission,[13] suggesting that it is easier for the patient to detect a flare once remission has been achieved. The high sensitivity of patient-reported flares in detecting clinically significant flare underscored the potential clinical value; in 91% of visits with clinically significant flare, patients had reported a flare. The presence of patient-reported flares corresponded to increased inflammatory disease activity outcomes, including ultrasound scores and inflammatory markers. Similar associations have been previously reported and indicate that patient-reported flares reflect increased inflammatory disease activity despite differences between patients' and health professionals' perception of flares.[16 38–40]

The frequency of patient-reported flares was higher than clinically significant flares, which resulted in a relative low likelihood of 46% of observing a clinically significant flare at the same visit, supporting that patients' threshold for experiencing a flare tends to be lower

compared with that of the healthcare provider.[41] The lower patient threshold for reporting a flare may result in increased utilisation of healthcare resources, such as extra clinical visits. However, considering that one in two patients who reported a flare required a treatment escalation, using the patient-reported flare questionnaire to select patients for a clinical visit, could be an effective allocation of resources.

In patient-reported flares, which were not verified as clinically significant flares, we demonstrate a small, but statistically significant increase in clinical disease activity measures, inflammatory markers and physician's global assessment of disease activity from the previous visits, which indicate a worsening in disease activity. Furthermore, 23% of these patients experienced a clinically significant flare at the next visit or later during the 12-month follow-up. These findings could indicate that patient-reported flares could contribute to identification of patients at risk of future flares, as has recently been suggested in a validation study of the French FLARE-RA questionnaire from Doumen *et al*[39]

We show that a negative patient-reported flare status had a strong concurrence with the clinical evaluation, with a negative predictive value of 99%. In line with previous observations, our results could indicate that a negative patient-reported flare assessment could be highly precise in ruling out a clinically significant flare.[13 40] Likelihood ratios in our data provided support of the abilities of patient-reported flare status to both rule in and out a clinically significant flare, with a positive likelihood ratio of >10, and negative likelihood ratio of 0.1.[33]

In 5 of 578 (1%) visits where patients did not report a flare, a clinically significant flare was registered. These patients could potentially be at risk of having undetected flares if followed by remote monitoring, although we do not know if the patient given more time would have reported a flare or if the flare would have resolved without intervention. Due to the limited number of patients, further characteristics of this group of patients were not possible. Assessment of health literacy skills and patient education regarding symptoms and signs of flare and when to report a flare are important before implementation of a flare questionnaire in remote monitoring.[18 42–44]

Patient-reported levels of joint pain, disease activity, functional disability, fatigue, sleep disturbances and emotional distress were overall low at baseline in correspondence with the strict inclusion criteria. We observed a significant deterioration in patient-reported outcomes associated with patient-reported flares, demonstrating a broad impact on multiple symptoms, including fatigue, physical function, sleep and emotional well-being. Pain has been acknowledged as a dominant symptom during a flare and has been identified as the main driver in patient-reported flares, and our findings are consistent with these observations.[38 45 46] In the ARCTIC REWIND trials, patients were asked to contact the study site if they suspected a disease activity flare, leading 28% of patient-reported flares to be reported at extra visits related to a potential flare. The majority of patient-reported flares (60%) were reported to last longer than 14 days, indicating that most patient-reported flares were more than day-to-day fluctuations in symptoms.

A limitation of the current study is that results from these RA patients in sustained remission followed in a strict trial setting with frequent study visits may not be generalisable to patients with RA in, for example, stable low disease activity or in different cultural settings. Furthermore, these patients may have been better educated regarding flare than the average RA population due to the participation in the current trial. The generalisability to patients followed with remote care might also be limited by the organisation of the data collection, where patients only filled out the flare questionnaire when attending a clinical visit. However, by censoring data after the first clinically significant flare, our analyses exclusively contain data from patients who could be considered eligible for remote monitoring. In addition, comorbidities, such as fibromyalgia and depression, which could potentially influence the perception of symptoms and lead to discrepancies between patient-reported flares and clinically significant flares, were infrequent in our study.[47–49] We do not know if the open design has influenced the reporting of flare, but study personnel were thoroughly instructed to record flares in a similar manner in both groups. A strength of the study was the extensive, longitudinal data material with little data missing. The clinically verified flare status allowed us to compare patient-reported flare to clinically significant flares with subsequent treatment escalations. The definition of clinically significant flare could be based on either DAS/swollen joints or consensus between patient and rheumatologist. However, flares deemed as clinically significant led to subsequent intensification of DMARD therapy in 91%, and short-term glucocorticoids, intra-articular injections or NSAIDs in the remaining flares, indicating that clinicians found the disease activity to warrant active treatment. Previous reviews of the flares based on agreement between patient and rheumatologist showed that such flares could typically include inflammation in joints not included in the DAS44 joint examination, large increases in inflammatory markers or inflammation on ultrasound examination identified in joints not interpreted as swollen by clinical evaluation.[19 20]

In conclusion, our study found a high agreement between patient-reported flare status and whether patients were found to have a clinically significant flare. This indicates that the patient-reported flare status might contribute to both the detection and exclusion of clinically significant flares in patients with RA in sustained remission. According to our analyses, patient-reported flares after achievement of RA remission reflect increased inflammatory disease activity, and furthermore, patient-reported flares which are not verified as clinically significant flares might represent early risk markers of future flares. Hence, patient-reported flare could contribute

to early flare detection and treatment intervention, ultimately preventing disease progression.

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Contributors All authors were involved in drafting the article or revising it critically for important intellectual content and approved the final manuscript to be submitted and agreed to be accountable for all aspects of the work. Conception and design of the study: KH, JS, NPS, EAH, SL and A-BA. Acquisition of data: NPS, EAH, SL, A-BA. Analysis and interpretation of data: KH, NPS, JS, KEK, LBN, EM, TU, DvdH, DHS, EAH, SL and A-BA. KH is responsible for the overall content and accepts full responsibility for the work as the guarantor. SL and A-BA are shared last authorship.

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