Pain and Self-reported Swollen Joints Are Main Drivers of Patient-reported Flares in Rheumatoid Arthritis: Results from a 12-month Observational Study

Dorota Kuettel, Jette Primdahl, Ulrich Weber, Lene Terslev, Mikkel Østergaard, Randi Petersen, Andreas Kristian Pedersen, Sören Möller, and Kim Hørslev-Petersen

ABSTRACT. ***Objective.*** To examine prospectively self-reported flare characteristics and their longitudinal association with disease activity and patient-reported outcomes (PRO) in patients with rheumatoid arthritis (RA).

Methods. Consecutive RA patients with 28-joint count Disease Activity Score based on C-reactive protein (DAS28-CRP) < 3.2 and no swollen joints were examined at baseline, Month 6, and Month 12. Assessments included joint counts, DAS28-CRP, visual analog scale–evaluator's global assessment (EGA), and PRO. Every third month, patients completed the Flare Assessment in Rheumatoid Arthritis and RA Flare Questionnaire, and disclosed self-management strategies. Flaring and non-flaring patients were compared and longitudinal associations between self-reported flare status (yes/no) and disease activity, PRO, and treatment escalation were explored.

Results. Among 80 patients with RA [74% females, mean (SD) age 63 (10) yrs, disease duration 11 (7) yrs, and baseline DAS28-CRP 1.9 (0.6)], 64 (80%) reported flare at least once during 12 months. Fifty-five percent of flares lasted less than 1 week. Common self-management strategies were analgesics (50%) and restricted activities (38%). Patients who reported being in flare had consistently higher disease activity measures and PRO compared to patients without flare. In a partly adjusted model, all flare domains, patient-reported swollen and tender joint counts and disease activity measures were associated with flares. In fully adjusted analyses, present flare was independently associated with pain (OR 1.85, 95% CI 1.34–2.60), patient-reported swollen joints (OR 1.18, 95% CI 1.03–1.36), and higher EGA (OR 1.15, 95% CI 1.04–1.28). Treatment escalation was associated with present flare ($p \leq 0.001$).

Conclusion. In RA, self-reported flares were frequent, mainly managed by analgesics, substantiated by higher disease activity measures, independently associated with pain and patient-reported swollen joints, and related to treatment escalation. (First Release July 1 2020; J Rheumatol 2020;47:1305–13; doi:10.3899/jrheum.190760)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PATIENT-REPORTED OUTCOMES FLARES

From the Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, Sønderborg; Institute of Regional Health Research, University of Southern Denmark, Odense; Hospital of Southern Jutland, University Hospital of Southern Denmark, Aabenraa; Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet – Glostrup, Glostrup; Open Patient data Explorative Network (OPEN), Odense University Hospital and Department of Clinical Research, University of Southern Denmark, Odense, Denmark.

This study was supported by the Danish Rheumatism Association, the University of Southern Denmark, the Region of Southern Denmark, and the Knud og Edith Eriksens Mindefond (Knud and Edith Eriksens Memorial Fund).

D. Kuettel, MD, PhD, Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, and Institute of Regional Health Research, University of Southern Denmark; J. Primdahl, MSN, PhD, Professor, Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, and Institute of Regional Health Research, University of Southern Denmark, and Hospital of Southern Jutland, University Hospital of Southern Denmark; U. Weber, MD, Associate Professor, Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, and Institute of Regional Health Research, University of Southern Denmark, and Hospital of Southern Jutland, University Hospital of Southern Denmark; L. Terslev, MD, PhD, Associate Professor, COPECARE, Center for Rheumatology and Spine Diseases, Rigshospitalet – Glostrup; M. Østergaard, MD, PhD, DMSc, Professor, COPECARE, Center for Rheumatology and Spine Diseases, Rigshospitalet – Glostrup; R. Petersen, MSN, Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark; A.K. Pedersen, MS, Hospital of Southern Jutland, University Hospital of Southern Denmark; S. Möller, MS, PhD, Associate Professor, OPEN, Odense University Hospital and Department of Clinical Research, University of Southern Denmark; K. Hørslev-Petersen, MD, DMSc, Professor, Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, and Institute of Regional Health Research, University of Southern Denmark.

Address correspondence to Dr. D. Kuettel, Danish Hospital for Rheumatic Diseases, University Hospital of Southern Denmark, Engelshøjgade 9A, DK-6400 Sønderborg, Denmark. E-mail: Dkuttel@danskgigthospital.dk, dkuettel@health.sdu.dk

Accepted for publication November 8, 2019.

Treatment of patients with rheumatoid arthritis (RA) aims at sustained remission or low disease activity (LDA)[1]. Owing to major advances in the treatment of RA in the last decades, these therapeutic objectives are realistic goals for many patients[2]. However, patients who have reached remission or LDA may still experience flares[3,4]. These fluctuations in disease activity are strongly associated with poor clinical outcomes, may lead to progression of radiographic joint damage and impaired function, and accelerate cardiovascular (CV) comorbidity[5,6,7,8].

Following the European League Against Rheumatism (EULAR) overarching principles for the treatment of patients with RA, shared decision making between the patient and the rheumatologist is a cardinal feature in disease management[1]. Hence, it is essential to integrate the patient's perspective into the flare definition. The concept of patient-reported flares has emerged as a major determinant in the disease trajectory with substantial effect on everyday life activities[9,10,11], and has been linked to functional impairment[4]. It is well established that patient-reported flares differ from one patient to another regarding duration, frequency, and symptom severity[3,12].

More recent international initiatives culminated in standardization of definition and measurement tools of flares[13,14,15,16]. Two questionnaires incorporating patient perspectives were developed in parallel; both aimed to identify flare domains that patients and health professionals considered important to be included in a measure of flare. The Outcome Measures in Rheumatology (OMERACT) RA Flare Group has developed the RA Flare Questionnaire (RA-FQ) and has defined RA flares as "episodes of increased RA disease activity accompanied by a cluster of symptoms of sufficient intensity and duration to require initiation of, change, or increase in therapy"[13,16,17,18]. A French group developed a self-administered instrument, the Flare Assessment in Rheumatoid Arthritis (FLARE-RA), to detect fluctuations in disease activity between rheumatology visits[19]. Both questionnaires have been validated in patients with RA[14,20,21]. However, a threshold for flare detection was not established at the initiation of the study for both questionnaires. Flare domains have been shown to correlate with other patient-reported outcomes (PRO) measuring similar features when analyzed cross-sectionally[14,18,21]. Previous studies have addressed the predictors of clinical flares defined by the Disease Activity Score (DAS) flare definition[7,22]. Yet evidence is sparse regarding the relationship between clinical disease activity measures and flare domains upon patient-defined flare status and regarding clinical predictors and potential drivers of self-reported flares.

The objectives of our study were to describe characteristics and self-management strategies of self-reported flares in anticitrullinated peptide antibody (anti-CCP)– and/or rheumatoid factor (RF)-positive RA patients; to assess associations between self-reported present flare, other PRO, and clinical disease activity; and to investigate whether self-reported present flare is associated with escalation of medical treatment.

MATERIALS AND METHODS

Study design and participants. The FLARA study (FLAre-in-RA) is a prospective 1-year observational single-center study, where consecutive patients with RA were recruited from the outpatient clinic at the Danish Hospital for Rheumatic Diseases between August 2016 and June 2017.

Patients ≥ 18 years were eligible if they fulfilled the American College of Rheumatology (ACR) 1987 or ACR/EULAR 2010 criteria for RA[23,24], were RF- and/or anti-CCP–positive, had a 28-joint count DAS based on C-reactive protein (DAS28-CRP) < 3.2 and no clinically detectable swollen joints at baseline. Further requirements were stable disease-modifying antirheumatic drug (DMARD) treatment and no intraarticular glucocorticoid injections in the last 4 weeks prior to study entry.

The FLARA study was supported by the local patient research board and 1 member participated as a patient research partner. The study was approved by the regional ethics committee (The Regional Scientific Ethical Committees for Southern Denmark, S-20160027), and was conducted according to the Declaration of Helsinki 2013. Written informed consent was obtained from all participants.

Patient-reported flare definition. The flares were divided into present or past flare in relation to the time of completing the questionnaire. Present flare was assessed from the patient perspective by the anchor question: "Are you experiencing a flare of your RA at this time?" (yes/no) and this definition was considered the primary outcome of self-reported flare throughout the entire study.

Flare questionnaires and supplementary flare questions. Patients who reported to be in a flare, rated the flare severity on an 11-point numerical rating scale (NRS) and the flare duration (1–3, 4–7, 8–14, or > 14 days). Moreover, patients completed the RA-FQ consisting of 5 questions assessing pain, physical function, fatigue, stiffness, and participation over the past week on an NRS from 0 (none) to 10 (severe)[14,20]. A sum score across all items was calculated, ranging from 0 to 50. Further, patients indicated tender and swollen joints on a manikin sketch.

Past flares were identified by the question: "In the last three months (or at some time since the last visit): Do you think your RA has had a flare?" Response options were as follows: no; yes, once; and yes, more than once. This flare definition was applied to standardize the assessment of flare frequency during 1 year of followup but was not used as an outcome in any of the main analyses investigating associations between flare and other variables. Patients completed the FLARE-RA, consisting of 12 questions, and the total score was calculated, as the mean across all items, ranging from 0 (no flare) to 10 (maximum flare)[25,26].

Patients who reported either past or present flares completed supplementary questions as proposed by the OMERACT RA Flare Group about flare self-management strategies such as using analgesics, reducing activities, avoiding activities, behavioral approaches, using glucocorticoids, and calling the rheumatology clinic for help[15,27,28].

Patients completed the flare questionnaires when attending clinical visits at baseline, Month 6, and Month 12 after baseline, while at months 3 and 9, the questionnaires were either mailed electronically or sent as a hard copy, according to patients' preferences. A text message reminder was sent to all patients.

Other PRO. At the clinical visits at baseline, Month 6, and Month 12, participants were asked to complete visual analog scales (VAS) for pain, fatigue, and patient's global assessment (0–100). The Danish version of the Health Assessment Questionnaire was applied to assess physical function[29].

Clinical and laboratory assessments. In accordance with the EULAR recommendations for a core dataset to support observational research, these were recorded at baseline: age, sex, disease duration, ongoing

pharmacological therapy for RA, weight, height, and selected comorbidities (diabetes, hypertension, CV diseases, depression, osteoarthritis, cancer)[30].

At baseline, and months 6 and 12 after baseline, a rheumatologist or a rheumatology nurse carried out a clinical examination for a swollen and tender count in 28 joints (SJC28 and TJC28, respectively), CRP was collected, and DAS28-CRP was calculated. Evaluator's global assessment (EGA) was assessed by a VAS 0–100. The patients were tested for IgM-RF and anti-CCP positivity at baseline.

Escalation of medical treatment. The escalation of medical treatment was assessed at Month 6 and Month 12 and was defined as follows: initiation of or added and/or increased dosage of conventional DMARD (cDMARD), biological DMARD (bDMARD), or steroids, likewise treated as a binary variable (yes/no).

Statistical analysis. Descriptive statistics were presented as frequencies with percentages for categorical variables, and as means with SD for continuous variables. Self-management strategies in relation to flares were described. Depending on data distribution, parametric (2 sample t tests) or non-parametric (Wilcoxon rank-sum test) analyses were used to compare patients reporting present flare versus not in present flare. We used Fisher's exact test to investigate the differences between treatment escalation and self-reported flare status.

We were dealing with repeated measurements on the same subjects. Thus mixed-effects logistic regression analyses were used, with subject as a random effect, to analyze associations at all timepoints simultaneously. The analyses were performed with present flare status as a binary dependent variable and the following exploratory variables: disease activity measures (SJC28, TJC28, CRP, EGA). Likewise, the analyses were performed between present flare status and the following PRO: flare domains from RA-FQ (pain, function, fatigue, stiffness, and participation) and patient-reported swollen joints and tender joints. For the clinical explanatory variables, 3 timepoints corresponding to clinical visits were used in the analyses, while for PRO, all 5 timepoints were used.

Our analyses followed a 2-step approach: first analyses with a partly adjusted and subsequently fully adjusted model. In the partly adjusted model, we included 1 explanatory variable at a time, while we included all explanatory variables simultaneously in the fully adjusted model to elucidate the independent associations. We considered age, sex, disease duration at baseline, and comorbidities as potential confounders and included them as covariates in both the partly and the fully adjusted models. Comorbidities were categorized into 3 categories: none, 1, and more than 1. To account for the time-varying variable, time (timepoints for clinical visits/patients' reports) was treated as a categorical variable and was included in all models.

For all analyses, we reported adjusted OR estimates with 95% CI. A 95% CI excluding 1 was considered statistically significant (i.e., $p < 0.05$). All analyses were carried out using Stata version 15.0 (StataCorp.).

RESULTS

Eighty RA patients with mean (SD) disease duration of 11 (7) years were included. Demographic and baseline characteristics are shown in Table 1. Mean (SD) age was 63 (10) years, 74% were female, and baseline DAS28-CRP 1.9 (0.6). Patients had low levels of self-reported disease activity, only 18/80 (23%) patients had pain (VAS) above 30 mm. The majority of patients (66/80, 82%) were receiving cDMARD, 41/80 (51%) received 2 concomitant cDMARD while none was on triple therapy. Comorbidities were common: hypertension 23/80 (29%), osteoarthritis (OA) 21/80 (26%), depression 9/80 (11%), diabetes 8/80 (10%), other CV diseases 3/80 (4%), and malignancies 4/80 (5%).

Numbers of patients at each followup timepoint were 80 (100%) at 3 months, 79 (99%) at 6 months, and 78 (97.5%) at 9- and 12-month followups.

Table 1. Baseline characteristics of 80 patients included in the study.

Characteristics	Mean (± SD) or n (%)
Age, yrs	63 (± 10)
Female/male	59/21 (74/26)
Disease duration, yrs	11 (± 7)
Ongoing treatment	
cDMARD	66 (82.5)
MTX	55 (69)
MTX dose, mg/week	18 (± 5)
bDMARD	2 (2.5)
bDMARD + cDMARD	7 (8.8)
None	4 (5)
Glucocorticoids	1 (1.3)
Erosive RA	45 (56)
Comorbidities*	
None	42 (52.5)
1	22 (27.5)
> 1	16 (20)
BMI, mean (SD)	28.8 (8.3)
Anti-CCP+	75 (94)
IgM-RF+	75 (94)
Anti-CCP+ and/or IgM-RF+	80 (100)
DAS28-CRP	1.9 (± 0.6)
CRP, mg/l	4.8 (± 7.7)
TJC28	0.5 (± 1.2)
SJC28	0 (± 0)
Patient-reported TJC28	1.2 (± 2.8)
Patient-reported SJC28	0.1 (± 0.5)
Pain (VAS)	17.3 (± 18)
Fatigue (VAS)	30 (± 24.4)
PtGA (VAS)	21 (± 20.7)
EGA (VAS)	3.8 (± 3.4)
HAQ	0.5 (± 0.5)
FLARE-RA (range 0–10)	1.5 (± 1.8)
RA-FQ (range 0–50)	9.5 (± 9.2)

Values are mean (± SD) scores or n (%) of demographic, clinical, patient-reported, laboratory characteristics at baseline. * Comorbidities: diabetes, hypertension, other cardiovascular diseases, depression, osteoarthritis, or cancer. cDMARD: conventional disease-modifying antirheumatic drug; MTX: methotrexate; bDMARD: biological DMARD; RA: rheumatoid arthritis; BMI: body mass index; anti-CCP: anticyclic citrullinated peptide antibody; RF: rheumatoid factor; DAS28-CRP: 28-joint count Disease Activity Score based on C-reactive protein; VAS: visual analog scale; PtGA: patient's global assessment; EGA: evaluator's global assessment; TJC28: tender joint count in 28 joints; SJC28: swollen joint count in 28 joints; HAQ: Health Assessment Questionnaire; FLARE-RA: Flare Assessment in Rheumatoid Arthritis questionnaire; RA-FQ: OMERACT (Outcome Measures in Rheumatology) Rheumatoid Arthritis Flare Questionnaire.

Flare characteristics. The patients completed 385 (96%) of the RA-FQ and 379 (95%) of the FLARE-RA questionnaires. Eighty percent (64/80) of the patients reported to have experienced a flare during the 12 months' followup. Thirty-six percent (29/80) reported present flare and 71% (57/80) reported past flare at least once during 12 months. The number of present flares ranged between 1 (18 patients) and 4 (1 patient), with a mean (SD) of 1.55 (0.82) per patient.

The majority of present flares (40%) had lasted 1–3 days, 15% had lasted 4–7 days, 18% remained for 8–14 days, and 27% lasted longer than 2 weeks when completing the questionnaires. The mean (SD) flare severity was 4.9 (3.0).

Metacarpophalangeal (MCP) joints were most frequently reported as being swollen or tender at the time of flares (Table 2).

Self-management strategies. Patients managed their flares through a wide variety of strategies, the most common being the use of analgesics (50%) and to reduce activities (38%). Avoiding activities and behavioral approaches (massage, attending physical therapy, exercise, applying warm/cold pack) were used in 23% and 19% of patients reporting a flare, respectively. Only a minority (15%) of the patients did not change their behavior (i.e., did not do anything differently) when they experienced a flare. The least common strategies were to call their rheumatologist/rheumatology nurse for help (11%) or to take glucocorticoids (3%). However, when reporting prolonged flares > 14 days at Month 3 and Month 9, four out of 5 patients contacted the outpatient clinic for help, which resulted in treatment escalation in 3 patients.

Comparison of patients in present flare versus not in present flare. Patients reporting present flare had higher clinical disease activity measures and higher levels of PRO, including both flare questionnaires, than patients currently not in flare. Table 3 shows the differences by flare status in variables collected at the clinical visits, while Table 4 presents differences in PRO collected every third month. All differences between flaring and non-flaring patients were statistically significant except for CRP, and fatigue at Month 6 and Month 9 (Table 3 and Table 4).

Change scores from baseline to clinical visit were higher for flaring patients compared to non-flaring patients at Month 6 and Month 12, respectively (Appendix 1).

Associations across all clinical visits between self-reported present flare and measures of disease activity. Present flare was longitudinally associated with higher disease activity measures: SJC28, TJC28, CRP, and EGA in the partly adjusted model as illustrated in Table 5. In the fully adjusted model, only EGA was significantly associated with present flare with adjusted OR (95% CI) of 1.15 (1.04–1.28, $p < 0.01$).

Associations across all timepoints between self-reported present flare and PRO. Present flare was significantly associated with all RA-FQ flare domains, as well as with patient-reported tender and swollen joints, in the partly adjusted model (all p values < 0.001; Table 5). In the fully adjusted model, only pain and patient-reported swollen joints remained significantly associated with present flare [adjusted OR 1.85 (95% CI 1.34–2.60), $p < 0.001$; and 1.18 (95% CI 1.03–1.36), $p < 0.05$, respectively].

Associations with escalation of medical treatment at Month 6 and Month 12. At Month 6, 63% of flaring patients and 8% of non-flaring patients ($p = 0.001$), and at Month 12, 60% of flaring patients and 6% of non-flaring patients ($p < 0.0001$), were intensified in medical treatment (Table 6). None of the changes were induced by side effects.

DISCUSSION

Our prospective study over 12 months in patients with RA in LDA showed that self-reported flares were frequent, mostly short-lived, and triggered a variety of self-management strategies. MCP joints were most frequently affected by flares. Higher joint counts, CRP, and EGA were associated with greater odds of present flare, suggesting that patient-reported flares are a marker of increased inflammation. Patient-reported flares were mainly driven by pain and self-reported swollen joints, and were associated with treatment escalation.

In our study, 36% of patients reported present flare and 71% reported past flare at least once over 12 months. These findings are in accordance with the results of an observational study in patients with established RA, where the frequency of self-reported flares ranged from 54 to 74% over a 6-month period[3]. In an online survey among 403 patients with RA, 95% reported a transient flare at least once during the previous 12 months[12]. Despite different anchor questions to detect flares and various periods of recall, previous reports and our study lend support to the notion that self-reported flares are common in RA patients. The majority (55%) of present flares were reported to last less than 1 week, consistent with the findings in a recent report on flares in RA[31].

We observed that the small joints of the hands were the primary target of flare, which has not been reported previously, to the best of our knowledge. A previous study showed

Table 2. Number of patients reporting swollen/tender joints across all visits when reporting flare.

Subjects with Affected Joints, n	Shoulder		Elbow		Wrist		MCP		PIP		Knee		Ankle		MTP	
	Swollen	Tender	Swollen	Tender	Swollen	Tender	Swollen	Tender	Swollen	Tender	Swollen	Tender	Swollen	Tender	Swollen	Tender
≥ 1 joint	8	17	4	13	17	24	20	27	17	17	9	11	9	11	17	13
≥ 2 joints	4	9	1	3	5	10	14	15	7	6	4	6	4	5	6	6
≥ 3 joints	NA	NA	NA	NA	NA	NA	12	12	4	2	NA	NA	NA	NA	3	4

MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint; MTP: metatarsophalangeal joint; NA: not applicable.

Table 3. Characteristics of flaring versus non-flaring patients* at 6 and 12 months' followup.

Characteristics	Month 6, n = 79			Month 12, n = 78		
	Flare, n = 8	No Flare, n = 65	p	Flare, n = 15	No Flare, n = 62	p
DAS28-CRP	3.3 (1.6)	2.1 (0.8)	< 0.05	3.7 (1.6)	2.0 (0.7)	< 0.0001
CRP, mg/l	9.7 (16.9)	4.3 (6.3)	0.42	22.4 (34.9)	4.2 (4.9)	0.07
TJC28	4.6 (6.3)	1.2 (2.2)	< 0.05	5.7 (8.3)	1.0 (2.5)	< 0.0001
SJC28	1.1 (2.0)	0.1 (0.5)	< 0.01	1.7 (2.9)	0.3 (1.4)	< 0.001
EGA (VAS)	16.5 (17.5)	4.6 (3.8)	< 0.05	20.3 (19.4)	5.7 (6.2)	< 0.0001
Pain (VAS)	50.6 (24.3)	18.2 (18.6)	< 0.01	45.6 (31.7)	16.3 (15.8)	< 0.01
Fatigue (VAS)	41.6 (23.1)	26.9 (24.6)	0.09	46.7 (31.1)	27 (21.7)	< 0.05
PtGA (VAS)	47.8 (30.2)	18.0 (19.2)	< 0.01	44.1 (30.9)	19.0 (19.7)	< 0.01
HAQ	0.9 (0.6)	0.5 (0.6)	< 0.01	0.8 (0.6)	0.4 (0.5)	< 0.05

Mean (SD) scores of clinical, patient-reported, and laboratory characteristics at months 6 and 12 of followup. * Based on the question "Are you experiencing a flare of your RA at this time?" (yes/no). Missing flare reports at Month 6: n = 6, and at Month 12: n = 1. DAS28-CRP: 28-joint count Disease Activity Score based on C-reactive protein; TJC28: tender joint count in 28 joints; SJC28: swollen joint count in 28 joints; EGA: evaluator's global assessment; VAS: visual analog scale; PtGA: patient's global assessment; HAQ: Health Assessment Questionnaire.

Table 4. Patient-reported outcomes in flaring vs non-flaring* patients across all followup timepoints.

Characteristics	Month 3			Month 6			Month 9			Month 12		
	Flare, n = 8	No Flare, n = 72	p	Flare, n = 8	No Flare, n = 65	p	Flare, n = 9	No Flare, n = 66	p	Flare, n = 15	No Flare, n = 62	p
Flare questionnaires												
FLARE-RA total score (0–10)	5.6 (2.8)	1.8 (1.6)	0.001	4.5 (2.5)	1.7 (2)	0.002	5.2 (2.8)	1.8 (1.9)	0.001	4.7 (2.3)	1.5 (1.8)	< 0.0001
RA-FQ total score (0–50)	29 (12.3)	11.5 (9.3)	< 0.0001	25.3 (13.6)	10.5 (9.6)	0.002	24.4 (14.6)	10.8 (9.8)	0.003	22.6 (11.7)	8.6 (7.7)	< 0.0001
RA-FQ flare domains												
Pain	6.6 (2.8)	2.5 (2.1)	< 0.0001	5.9 (2.8)	2.3 (2.1)	0.001	5.6 (2.6)	2.2 (2)	0.001	5.3 (2.6)	1.5 (1.5)	< 0.0001
Function	5.9 (3.1)	2.2 (2.1)	0.002	5.9 (2.8)	1.9 (1.9)	< 0.0001	4.6 (3.2)	2.0 (2.2)	0.009	4.5 (2.6)	1.7 (1.6)	< 0.0001
Fatigue	6.1 (2.9)	2.8 (2.5)	0.002	4.4 (3.4)	2.7 (2.6)	0.11	4.7 (3.2)	2.7 (2.4)	0.055	4.6 (2.9)	2.4 (2.3)	0.007
Stiffness	5.5 (2.8)	2.3 (2)	0.002	5.3 (3.1)	2.1 (2.2)	0.006	4.8 (3.1)	2.2 (2)	0.009	4.7 (2.6)	1.7 (1.7)	< 0.0001
Participation	5.6 (2.6)	1.8 (1.9)	0.001	3.9 (3.4)	1.7 (2.2)	0.031	4.9 (2.8)	1.8 (2.1)	0.001	3.6 (2.4)	1.3 (1.7)	0.002
Patient-reported joints												
TJC28	4.1 (4.5)	2.1 (3.3)	0.02	7.3 (7.5)	2.4 (4.6)	0.003	8.6 (6.6)	1.7 (3.4)	< 0.0001	5.4 (6.3)	1.5 (4)	< 0.0001
SJC28	3.6 (4.4)	1.1 (2.5)	0.001	5.6 (6.9)	0.9 (2.2)	0.003	5.1 (7.8)	0.4 (1.2)	< 0.0001	3.9 (4.5)	0.5 (1.4)	< 0.0001

*Based on the question "Are you experiencing a flare of your RA at this time?" (yes/no). Values are mean (SD) unless otherwise specified. FLARE-RA: Flare Assessment in Rheumatoid Arthritis questionnaire; RA-FQ: OMERACT (Outcome Measures in Rheumatology) Rheumatoid Arthritis Flare Questionnaire; TJC28: tender joint count in 28 joints; SJC28: swollen joint count in 28 joints.

that ultrasonography of the hands in patients with RA in clinical remission detected subclinical inflammation in > 90% of patients[32], and we speculate that subclinical inflammation depicted by sensitive imaging modalities might be a trigger of short-lived transient flares, especially in the small joints of the hand. This hypothesis needs to be examined in future studies. We have recently observed that patients who self-reported hand flares had increased inflammatory activity on ultrasonography as compared to the status when not in flare[33].

Previous reports about self-management strategies among flaring patients concur with our own observations: that the primary means of self-management among flaring patients have been analgesics and reducing activities, followed by avoiding activities and behavioral approaches[27,28]. The least common strategy has been the use of steroids and asking the rheumatology clinic for help, consistent with our results[12,27]. Rarely asking for external help during flaring was also observed in a recent study evaluating the effect of a nurse-led flare management intervention, wherein for the majority of flares (62%) patients preferred self-management rather than clinical visit (32% of flares) or nursing advice over the phone (6% of flares)[34].

We found that all the traditional disease activity measures such as joint counts, CRP, or EGA were associated with present flare in the partly adjusted model. However, EGA, which is thought to depict clinical signs of inflammation, was the only independently associated item in the fully adjusted model[35].

Among PRO, all RA-FQ flare domains and patient-reported joints were associated with present flare, while the association was strongest for pain. This was expected because pain was recognized as a critical feature in defining a flare already at OMERACT 9 in 2008, when the process

Table 5. Mixed-effects logistic regression examining associations across all timepoints* with self-reported present flare as outcome variable.

Explanatory Variables	Partly Adjusted Model** OR (95% CI)	p	Fully Adjusted Model** OR (95% CI)	p
Disease activity measures				
EGA (VAS)	1.16 (1.08–1.25)	< 0.001	1.15 (1.04–1.28)	< 0.01
TJC28	1.31 (1.10–1.55)	< 0.01	1.02 (0.83–1.26)	0.85
SJC28	2.04 (1.25–3.35)	< 0.01	0.89 (0.48–1.68)	0.72
CRP	1.08 (1.02–1.14)	< 0.01	1.02 (0.96–1.08)	0.52
RA-FQ flare domains and patient-reported joints				
Pain	1.84 (1.52–2.22)	< 0.001	1.85 (1.34–2.60)	< 0.001
Function	1.71 (1.40–2.10)	< 0.001	0.88 (0.64–1.21)	0.44
Fatigue	1.45 (1.23–1.71)	< 0.001	0.91 (0.69–1.18)	0.47
Stiffness	1.73 (1.38–2.17)	< 0.001	0.94 (0.67–1.32)	0.73
Participation	1.65 (1.35–2.02)	< 0.001	1.14 (0.86–1.52)	0.37
Patient-reported TJC28	1.18 (1.08–1.27)	< 0.001	1.00 (0.92–1.09)	0.94
Patient-reported SJC28	1.39 (1.21–1.60)	< 0.001	1.18 (1.03–1.36)	< 0.05

* For clinical variables at clinical visits: baseline, Month 6, and Month 12; for patient-reported outcomes in 5 timepoints: baseline, months 3, 6, 9 and 12. ** All models are adjusted for age, sex, disease duration at baseline, and comorbidities, with subject as a random effect and timepoint treated as a categorical variable. EGA: evaluator's global assessment; VAS: visual analog scale; TJC28: tender joint count in 28 joints; SJC28: swollen joint count in 28 joints; CRP: C-reactive protein; RA-FQ: OMERACT (Outcome Measures in Rheumatology) Rheumatoid Arthritis Flare Questionnaire.

Table 6. Escalation from previous visit in antirheumatic treatment by flare status.

Escalation in Antirheumatic Treatment, n	Month 6		Month 12	
	Flare, n = 8 5 (63%)	No Flare, n = 65 5 (8%)	Flare, n = 15 9 (60%)	No Flare, n = 62 4 (6%)
MTX* added or increased	1	2	3	1
Non-MTX cDMARD added or increased	2	2	2	2
MTX and non-MTX DMARD increased	1	0	0	0
Glucocorticoids** added or increased	0	1	2	0
bDMARD added or increased	0	0	0	1
Physician intention to intensify but not initiated (e.g., declined by patient)	1	0	2	0

* Also change from oral to subcutaneous. ** Per oral, intramuscular, or intraarticular. bDMARD: biological disease-modifying antirheumatic drug; cDMARD: conventional DMARD; MTX: methotrexate.

to develop a flare definition was initiated[13]. Pain was also found to be a key determinant of flare in a study of patient perspective on flare[9].

At OMERACT 9, the investigator breakout groups recognized that swollen and tender joint counts were essential features to be included in an overall flare definition, while the patients' breakout group did not necessarily deem synovitis as relevant[13]. Similarly, in a study that aimed to develop a tool to identify RA flare, not all patients mentioned joint swelling as an item to consider when defining a flare[19]. We observed, however, that among patients reporting to be currently in flare, patient-reported swollen joints were more strongly associated with present flare status than patient-reported tender joints, and in the fully adjusted model, patient-reported swollen joints remained independently associated with flare, while patient-reported tender joints did not. In a recent study, patients with predominantly tender joints had lower levels of inflammation as defined by ultrasonography than patients with predominantly swollen joints[36]. Our finding, that patients weighted swollen joints higher than tender joints while reporting a flare, adds to the evidence that patient-reported flares may indeed reflect a higher burden of inflammation.

It has previously been speculated that comorbid conditions may influence patients' self-report of flare[37]. Depression may interfere with endogenous pain inhibition and enhance pain sensitivity, which is known to have a longterm effect on pain-related outcomes[38]. In OA, peripheral joint damage is thought to be one of the most important causes of pain[39]. Remarkably, in our sample self-reported flare was not associated with comorbid conditions.

We observed that patient-reported flare was associated with escalation of medical treatment. This is in line with the OMERACT flare definition, which aims at identifying clinically relevant, inflammatory flares[13,16]. Previously, the rheumatologist's intention to change/intensify a treatment has been used as a proxy for RA flare[22,40].

The FLARA study was neither intended nor designed

to validate the existing flare questionnaires, but to investigate which patient-reported and disease activity measures were associated with self-reported status of being in flare. We examined associations between RA-FQ flare domains because this questionnaire aims to detect present flares, and we recognize the relevance of the items from the FLARE-RA, which seeks to record exacerbation that occurred between 2 visits to a rheumatology clinic and queries 12 flare domains within the preceding 3-month period. Potential associations between the FLARE-RA domains and recent or current flares were beyond the scope of our present study.

Our study has several strengths, including prospective data collection and very low attrition rate, resulting in minimal missing data. A methodological strength is that we used mixed-effects logistic regression analyses, which is appropriate for repeated measurements, because it accounts for within-subject correlations, because we were dealing with repeated observations in the same individuals. We did not calculate lags because the timepoints for serial assessment were specified *a priori*. However, we included the time-varying aspect in all the models.

Limitations include the single-center design, and the sample selection restricted to patients with RA who were anti-CCP– and/or RF-positive, conditions thought to herald a worse prognosis[41] but that may compromise the generalizability of our findings. However, flare characteristics in our sample are comparable to previous reports, including multicenter studies recruiting the broad range of patients with RA. We used an anchor question to identify a flare and left this decision to the patient's discretion. For analysis of our study, no validated threshold of the sum score to detect a flare was available for the RA-FQ. Only very recently, candidate thresholds were proposed for the RA-FLARE[42]. The aim of the analysis of the PRO was to elucidate which of the individual flare domains were the most important drivers to the notion of the patients that they were experiencing a flare. We did not use a clinician flare definition as a standard to patient-reported flare, leaving our results susceptible to single-source bias. However, self-reported flare was also associated with clinical disease activity measures.

In this 1-year followup study of patients with RA in LDA or remission, flares were frequent, triggered a broad range of self-management strategies, and were substantiated by increased disease activity measures. Patients weighted the effect of swollen joints higher than that of tender joints at the time of flare, and self-reported flare was related to escalation of medical treatment. Our findings add support to the notion that patient-reported flares may reflect the inflammatory burden of RA, and can guide treatment modification in practice.

ACKNOWLEDGMENT

We thank all patients who participated in this study, along with the patient research partner. We thank research secretary Kirsten Frøhlich and research radiographer Henning Jakobsen, and the Danish Hospital for Rheumatic Diseases for logistical support. We also thank the staff of the hospital for assistance with recruitment of participants.

REFERENCES

1. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-77.
2. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis 2016;75:16-22.
3. Bykerk VP, Shadick N, Frits M, Bingham CO 3rd, Jeffery I, Iannaccone C, et al. Flares in rheumatoid arthritis: frequency and management. A report from the BRASS registry. J Rheumatol 2014;41:227-34.
4. Kuettel D, Primdahl J, Christensen R, Ornbjerg LM, Horslev-Petersen K. Impact of patient-reported flares on radiographic progression and functional impairment in patients with rheumatoid arthritis: a cohort study based on the AMBRA trial. Scand J Rheumatol 2018;47:87-94.
5. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36-42.
6. Myasoedova E, Chandran A, Ilhan B, Major BT, Michet CJ, Matteson EL, et al. The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. Ann Rheum Dis 2016;75:560-5.
7. Bechman K, Tweehuysen L, Garrood T, Scott DL, Cope AP, Galloway JB, et al. Flares in rheumatoid arthritis patients with low disease activity: predictability and association with worse clinical outcomes. J Rheumatol 2018;45:1515-21.
8. Markusse IM, Dirven L, Gerards AH, van Groenendael JH, Ronday HK, Kerstens PJ, et al. Disease flares in rheumatoid arthritis are associated with joint damage progression and disability: 10-year results from the BeSt study. Arthritis Res Ther 2015;17:232.
9. Hewlett S, Sanderson T, May J, Alten R, Bingham CO 3rd, Cross M, et al. 'I'm hurting, I want to kill myself': rheumatoid arthritis flare is more than a high joint count--an international patient perspective on flare where medical help is sought. Rheumatology 2012;51:69-76.
10. Flurey CA, Morris M, Richards P, Hughes R, Hewlett S. It's like a juggling act: rheumatoid arthritis patient perspectives on daily life and flare while on current treatment regimes. Rheumatology 2014;53:696-703.
11. Kirwan JR, Hewlett SE, Heiberg T, Hughes RA, Carr M, Hehir M, et al. Incorporating the patient perspective into outcome assessment in rheumatoid arthritis-progress at OMERACT 7. J Rheumatol 2005;32:2250-6.
12. Berthelot JM, Preiss P, Langiller M, Guillemin F, Fautrel B. Frequency, severity, and duration of transient flares in rheumatoid arthritis: A survey of 403 patients [abstract]. Ann Rheum Dis 2014;73:274-5.
13. Bingham CO 3rd, Pohl C, Woodworth TG, Hewlett SE, May JE, Rahman MU, et al. Developing a standardized definition for disease "flare" in rheumatoid arthritis (OMERACT 9 Special Interest Group). J Rheumatol 2009;36:2335-41.
14. Bykerk VP, Bingham CO, Choy EH, Lin D, Alten R, Christensen R, et al. Identifying flares in rheumatoid arthritis: reliability and construct validation of the OMERACT RA Flare Core Domain Set. RMD Open 2016;2:e000225.
15. Bykerk VP, Lie E, Bartlett SJ, Alten R, Boonen A, Christensen R, et al. Establishing a core domain set to measure rheumatoid arthritis

flares: report of the OMERACT 11 RA flare Workshop. J Rheumatol 2014;41:799-809.
16. Alten R, Pohl C, Choy EH, Christensen R, Furst DE, Hewlett SE, et al. Developing a construct to evaluate flares in rheumatoid arthritis: a conceptual report of the OMERACT RA Flare Definition Working Group. J Rheumatol 2011;38:1745-50.
17. Bingham CO 3rd, Alten R, Bartlett SJ, Bykerk VP, Brooks PM, Choy E, et al; OMERACT RA Flare Definition Working Group. Identifying preliminary domains to detect and measure rheumatoid arthritis flares: report of the OMERACT 10 RA Flare Workshop. J Rheumatol 2011;38:1751-8.
18. Bartlett SJ, Bykerk VP, Cooksey R, Choy EH, Alten R, Christensen R, et al. Feasibility and domain validation of rheumatoid arthritis (RA) flare core domain set: report of the OMERACT 2014 RA Flare Group Plenary. J Rheumatol 2015;42:2185-9.
19. Berthelot JM, De Bandt M, Morel J, Benatig F, Constantin A, Gaudin P, et al; STPR group of French Society of Rheumatology. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the 'FLARE' instrument. Ann Rheum Dis 2012;71:1110-6.
20. Bartlett SJ, Barbic SP, Bykerk VP, Choy EH, Alten R, Christensen R, et al. Content and construct validity, reliability, and responsiveness of the rheumatoid arthritis flare questionnaire: OMERACT 2016 Workshop report. J Rheumatol 2017;44:1536-43.
21. Fautrel B, Morel J, Berthelot JM, Constantin A, De Bandt M, Gaudin P, et al; STPR Group of the French Society of Rheumatology. Validation of FLARE-RA, a self-administered tool to detect recent or current rheumatoid arthritis flare. Arthritis Rheumatol 2017;69:309-19.
22. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis 2012;71:1316-21.
23. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
24. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
25. de Thurah A, Maribo T, Stengaard-Pedersen K. Patient self-assessment of flare in rheumatoid arthritis: criterion and concurrent validity of the flare instrument. Clin Rheumatol 2016;35:467-71.
26. Maribo T, de Thurah A, Stengaard-Pedersen K. Patient-self assessment of flare in rheumatoid arthritis: translation and reliability of the flare instrument. Clin Rheumatol 2016;35:1053-8.
27. Bartlett SJ, Bingham CO, Lin D, Boire G, Hitchon CA, Haraoui B, et al. How patients self-manage rheumatoid arthritis flares: findings from CATCH [abstract]. Ann Rheum Dis 2015;74:792-3.
28. Bartlett S, Bingham CO III, Lin D, Andersen K, Boire G, Hitchon C, et al. Working harder to stay in control: patient reports of flare in early RA are associated with higher disease activity and more intensive self management [abstract]. Arthritis Rheumatol 2015;67 Suppl 10:2277.
29. Thorsen H, Hansen TM, McKenna SP, Sorensen SF, Whalley D. Adaptation into Danish of the Stanford Health Assessment Questionnaire (HAQ) and the Rheumatoid Arthritis Quality of Life Scale (RAQoL). Scand J Rheumatol 2001;30:103-9.
30. Radner H, Chatzidionysiou K, Nikiphorou E, Gossec L, Hyrich KL, Zabalan C, et al. 2017 EULAR recommendations for a core data set to support observational research and clinical care in rheumatoid arthritis. Ann Rheum Dis 2018;77:476-9.
31. Mahmoud TG, Huang J, Frits M, Iannaccone C, Bykerk V, Bingham CO 3rd, et al. Correlates of successful rheumatoid arthritis flare management: clinician-driven treatment, home-based strategies, and medication change. J Rheumatol 2020;47:333-40.
32. Hammer HB, Kvien TK, Terslev L. Ultrasound of the hand is sufficient to detect subclinical inflammation in rheumatoid arthritis remission: a post hoc longitudinal study. Arthritis Res Ther 2017;19:221.
33. Kuettel D, Terslev L, Weber U, Østergaard M, Primdahl J, Petersen R, et al. Flares in rheumatoid arthritis: do patient-reported swollen and tender joints match clinical and ultrasonography findings? Rheumatology 2020;59:129-36.
34. Myasoedova E, Crowson CS, Giblon R, Schaffer D, Wright K, Matteson EL, et al. Optimization of flare management in patients with rheumatoid arthritis: results of a randomised controlled trial [abstract]. Ann Rheum Dis 2019;78:A236.
35. Desthieux C, Hermet A, Granger B, Fautrel B, Gossec L. Patient-physician discordance in global assessment in rheumatoid arthritis: a systematic literature review with meta-analysis. Arthritis Care Res 2016;68:1767-73.
36. Hammer HB, Michelsen B, Provan SA, Sexton J, Lampa J, Uhlig T, et al. Tender joint count may not reflect inflammatory activity in established rheumatoid arthritis patients - results from a longitudinal study. Arthritis Care Res 2020;72:27-35.
37. Filippou G, Sakellariou G, Scire CA, Carrara G, Rumi F, Bellis E, et al. The predictive role of ultrasound-detected tenosynovitis and joint synovitis for flare in patients with rheumatoid arthritis in stable remission. Results of an Italian multicentre study of the Italian Society for Rheumatology Group for Ultrasound: the STARTER study. Ann Rheum Dis 2018;77:1283-9.
38. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol 2011;7:216-24.
39. Gwilym SE, Pollard TC, Carr AJ. Understanding pain in osteoarthritis. J Bone Joint Surg Br 2008;90:280-7.
40. van der Maas A, den Broeder AA. Measuring flares in rheumatoid arthritis. (Why) do we need validated criteria? J Rheumatol 2014;41:189-91.
41. Hecht C, Englbrecht M, Rech J, Schmidt S, Araujo E, Engelke K, et al. Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. Ann Rheum Dis 2015;74:2151-6.
42. Myasoedova E, De Thurah A, Erpelding ML, Schneeberger EE, Maribo T, Citera G, et al. Definition and construct validation of clinically relevant cutoffs on the Flare Assessment in Rheumatoid Arthritis (FLARE-RA) questionnaire. Semin Arthritis Rheum 2020;50:261-5.

APPENDIX 1. Changes from baseline in clinical and patient-reported outcomes by flare status.

Change from Baseline	Month 6			Month 12		
	Flare, n = 8	No Flare, n = 65	p	Flare, n = 15	No flare, n = 78	p
DAS28-CRP	1.3 (1.6)	0.2 (0.5)	< 0.001	1.6 (1.6)	0.1 (0.7)	< 0.001
CRP, mg/l	6.2 (15.3)	-0.7 (7.0)	0.27	16.6 (29.3)	-0.5 (7.7)	< 0.01
TJC28	3.3 (6.5)	0.7 (1.9)	< 0.05	4.7 (9.0)	0.6 (2.3)	< 0.01
SJC28	1.1 (2.0)	0.1 (0.5)	< 0.001	1.7 (2.9)	0.3 (1.1)	< 0.001
EGA (0–100 VAS)	11.5 (16.3)	0.8 (4.7)	< 0.001	16.0 (18.5)	2.0 (6.6)	< 0.001
Pain (0–100 VAS)	37.0 (26.8)	-0.3 (16.3)	< 0.001	24.3 (31.7)	-0.4 (16.6)	< 0.001
Fatigue (0–100 VAS)	13.3 (27.0)	-4.2 (17.4)	< 0.05	13.1 (27.6)	-2.6 (19.7)	< 0.05
PtGA (0–100 VAS)	29.3 (32.9)	-3.6 (15.3)	< 0.001	17.5 (32.3)	-1.0 (17.9)	< 0.01
HAQ	0.3 (0.6)	0.0 (0.2)	< 0.05	0.1 (0.6)	0.0 (0.2)	0.28
FLARE-RA (0–10)	2.4 (3.5)	0.3 (1.9)	< 0.05	2.5 (2.3)	0.2 (2.1)	< 0.001
RA-FQ (0–50)	14.1 (15.0)	1.2 (7.2)	< 0.001	9.5 (10.6)	-0.2 (7.4)	< 0.001
Patient-reported TJC28	2.1 (7.8)	1.1 (3.3)	0.3	3.2 (7.9)	0.1 (3.1)	< 0.05
Patient-reported SJC28	3.6 (4.0)	0.5 (1.4)	< 0.01	2.9 (2.4)	0.4 (1.5)	< 0.001

Mean (SD) difference in scores of clinical, patient-reported, and laboratory characteristics. CRP: C-reactive protein; DAS28-CRP: 28-joint count Disease Activity Score based on CRP; TJC28: tender joint count in 28 joints; SJC28: swollen joint count in 28 joints; EGA: evaluator's global assessment; VAS: visual analog scale; PtGA: patient's global assessment; HAQ: Health Assessment Questionnaire; FLARE-RA: Flare in Rheumatoid Arthritis questionnaire; RA-FQ: OMERACT (Outcome Measures in Rheumatology) Rheumatoid Arthritis Flare Questionnaire.