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Pain and self-reported swollen joints are main drivers of patient-reported flares in rheumatoid arthritis. Results from a 12-months'observational study

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Running head: patient-reported flares

Abstract

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

Methods: Consecutive RA patients with DAS28CRP<3.2 and no swollen joints were examined at baseline, month 6 and 12. Assessments included joint counts, DAS28-CRP, visual analogue scale-evaluator global assessment (EGA) and PROs. Every third month, patients completed the FLARE-RA and RA Flare Questionnaire (RA-FQ), 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, PROs and treatment escalation were explored.

Results: Among 80 RA patients (74% females, mean(SD) age 63(10) years, disease duration 11(7) years and baseline DAS28-CRP 1.9(0.6)), 64(80%) reported flare at least once during 12 months. 55% of flares lasted less than one 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 PROs 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 1.30;2.60]), patient-reported swollen joints (OR 1.18 [1.03;1.36]), and higher EGA (OR 1.15 [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.

Introduction

Treatment of patients with rheumatoid arthritis (RA) is aiming at sustained remission or low disease activity (1). Due 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 low disease activity 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, impaired function and accelerate cardiovascular comorbidity (5-8).

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 in the flare definition. The concept of patient-reported flares has recently emerged as a major determinant in the disease trajectory with substantial impact on everyday life activities (9-11), 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).

Recent international initiatives culminated in standardization of definition and measurement tools of flares (13-16). Two questionnaires incorporating patient perspectives were developed in parallel; both aimed to identify flare domains which 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, 16-18). A French

group developed a self-administered instrument, the FLARE-RA, to detect fluctuations in disease activity between rheumatology visits (19). Both questionnaires have been validated in RA patients (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 (PROs) measuring similar features when analyzed cross-sectionally (14, 18, 21). Previous studies have addressed the predictors of clinical flares defined by the DAS-flare definition (7, 22). Yet evidence is sparse regarding 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 this study were to describe characteristics and self-management strategies of self-reported flares in anti-citrullinated peptide antibody (a-CCP) and/or rheumatoid factor (RF) positive RA patients; to assess associations between self-reported present flare, other PROs 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 one-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 / European League Against Rheumatism (EULAR) 2010 criteria for RA (23, 24),

were RF and/or anti-CCP positive, had a Disease Activity Score based on C-reactive protein (DAS28-CRP) <3.2 and no clinically detectable swollen joints at baseline. Further requirements were stable disease-modifying anti-rheumatic drug (DMARD) treatment and no intra-articular glucocorticoid injections in the last 4 weeks prior to study entry.

The FLARA study was supported by the local patient research board and one member participated as a patient research partner in the study. 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 five questions assessing pain, physical function, fatigue, stiffness and participation over the past week on a NRS from 0 (none) to 10 (severe) (14, 20). A sum score across all items

was calculated, ranging from 0 to 50. Furthermore, patients indicated tender and swollen joints (TJ and SJ, respectively) on a mannequin 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: no; yes, once; yes, more than once. This flare definition was applied to standardize the assessment of flare frequency during one year of follow-up, 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, calling the rheumatology clinic for help(15, 27, 28).

Patients completed the flare questionnaires when attending clinical visits at baseline, month 6 and 12 after baseline, while at month 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 Patient-reported outcomes (PROs)

At the clinical visits at baseline, month 6 and 12, participants were asked to complete visual analogue scales (VAS) for pain, fatigue and patient global assessment (0-100). The Danish version of the Health Assessment Questionnaire (HAQ) was applied to assess physical function (29).

Clinical and laboratory assessments

In accordance with the EULAR recommendations for a core data set to support observational research, age, gender, disease duration, ongoing pharmacological therapy for RA, weight, height and selected comorbidities (diabetes, hypertension, cardiovascular diseases, depression, osteoarthritis, cancer) were recorded at baseline (30).

At baseline, and month 6 and 12 after baseline, a rheumatologist or a rheumatology nurse carried out a clinical examination for a 28 swollen and tender joint count (SJC28 and TJC28, respectively), CRP was collected, and DAS28-CRP was calculated. Evaluator's global assessments (EGA) was assessed by a VAS 0-100. The patients were tested for IgM-RF and a-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: Initiation of or added and/or increased dosage of conventional DMARD (cDMARD); biologic 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 standard deviations (SD) for continuous variables. Self-management strategies in relation to flares were described. Depending on data distribution, parametric (two 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 Fishers 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 time points 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 PROs: flare domains from RA-FQ (pain, function, fatigue, stiffness and participation) and patient-reported SJ and TJ. For the clinical explanatory variables, 3 time points corresponding to clinical visits were utilized in the analyses, while for PROs all 5 time points were used.

Our analyses followed a two-step approach: first analyses with a partly adjusted and subsequently fully-adjusted model. In the partly adjusted model, we included one 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 three categories: none, one and more than one. To account for the time varying variable, time (time points for clinical visits/ patients' reports) was treated as a categorical variable and was included in all models.

For all analyses, we reported adjusted odds ratio (OR) estimates with 95% confidence intervals (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, Texas, USA).

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 two concomitant cDMARDs 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 cardiovascular diseases 3/80 (4%) and malignancies 4/80 (5%).

Numbers of patients at each follow-up time point were: 80 (100%) at 3 months, 79 (99%) at 6 months and 78 (97.5%) at 9- and 12-months follow-up.

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' follow-up. 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 8-14 days and 27% 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 by 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, 4 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 PROs, 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 PROs 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 (Supplementary table 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 to 1.28), ($p< 0.01$).

Associations across all time points between self-reported present flare and PROs

Present flare was significantly associated with all RA-FQ flare domains, as well as with patient-reported TJ and SJ, in the partly adjusted model, (all p-values < 0.001) (Table 5). In the fully adjusted model, only pain and patient-reported SJ remained significantly associated with present flare; adjusted OR [95% CI] 1.85 [1.34;2.60], ($p<0.001$) and 1.18 [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 low disease activity 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 RA patients, 95% reported a transient flare at least once during the past 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. Majority (55%) of present-flares were reported to last less than one 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 recent study showed that ultrasonography of the hands in RA patients 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 potential trigger of short-lived transient flares, especially in the small joints of the hand. This hypothesis needs to be explored 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 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 rheumatology clinic for help, consistent with our results (12, 27). The fact that patients do not often ask for external help when flaring was also observed in a recent study evaluating the effect of a nurse-led flare management intervention, where in majority of flares (62%) patients preferred self-management 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 PROs, all RA-FQ flare domains and patient-reported joints were associated with present flare, while the association was strongest for pain. This was expected since pain was recognized as a critical feature in defining a flare already at OMERACT 9 in 2008, where the process to develop a flare definition was initiated (13). Pain was also found to be a key determinant of flare in a study that explored the 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 which 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 stronger 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 then 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 long-term impact 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 explored associations between RA-FQ flare domains as this questionnaire aims to detect present flares, and we recognize the relevance of the items from the FLARE-RA, which seeks to capture exacerbation that occurred between two visits to a

rheumatology clinic and queries 12 flare domains within the preceding 3 months period. Potential associations between the FLARE-RA domains and recent or current flares were beyond the scope of the 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 utilized mixed effects logistic regression analyses, which is appropriate for repeated measurements, as it accounts for within-subject correlations, as we were dealing with repeated observations in the same individuals. We did not calculate lags as the time points for serial assessment were specified a priori. However, we included time varying aspect in all the models.

Limitations include the single center design, and the sample selection restricted to a-CCP and/or RF positive RA patients, which are thought to herald a worse prognosis (41) but 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 RA patients. We utilized 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 PROs 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 conclusion, in this one-year follow-up study of patients with RA in low disease activity or remission, flares were frequent, triggered a broad range of self-management strategies and were substantiated by increased disease activity measures. Patients weighted the impact of swollen joints higher than 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.

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Table 1 Baseline characteristics of 80 patients included in the study	
Age, years	63 (10)
Female/male (%)	59/21(74/26)
Disease duration, years	11 (7)
Ongoing treatment	
cDMARD (%)	66 (82.5)
Methotrexate (%)	55 (69)
Methotrexate dose (mg per 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)
One (%)	22 (27.5)
More than one (%)	16 (20)
BMI	28.8 (8.3)
Anti-CCP positive (%)	75 (94)
IgM RF positive (%)	75 (94)
Anti-CCP and/or IgM RF positive (%)	80 (100)
DAS28CRP	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)

Patient global (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)

Mean (SD) scores or counts (%) of demographic, clinical, patient-reported, laboratory characteristics at baseline; cDMARD, conventional disease modifying antirheumatic drug; bDMARD, biological disease modifying antirheumatic drug; *Comorbidities: diabetes, hypertension, other cardiovascular diseases, depression, osteoarthritis or cancer; BMI, body mass index; Anti-CCP, anti-cyclic citrullinated peptide antibody; RF, Rheumatoid factor; DAS28CRP, disease activity score based on 28 joints and CRP; CRP, C- reactive protein; VAS, visual analogue scale; EGA, evaluator global assessment; TJC, tender joint count in 28 joints; SJC, swollen joint count in 28 joints; HAQ, health assessment questionnaire; FLARE-RA, Flare Rheumatoid Arthritis questionnaire; RA-FQ, OMERACT (Outcome Measures in Rheumatology) Rheumatoid Arthritis Flare Questionnaire

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
≥ 1joint	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

Table 3. Characteristics of flaring vs non-flaring patients* at 6 and 12 months follow-up						
Characteristics	Month 6, n=79			Month 12, n=78		
	Flare, n=8	No flare, n=65	p-value	Flare, n=15	No flare, n=62	p-value
DAS28CRP	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
Patient global (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 month 6 and 12 of follow-up; DAS28CRP, disease activity score based on 28 joints and CRP; CRP, C- reactive protein; TJC28, tender joint count in 28 joints; SJC28, swollen joint count in 28 joints; EGA, evaluator global assessment; VAS, visual analogue scale; HAQ, health assessment questionnaire

*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, at month 12 n=1.

Table 4. Patient reported outcomes in flaring vs non-flaring* patients across all follow-up time points

Characteristics	Month 3			Month 6			Month 9			Month 12		
	Flare n=8	No flare n=72	p-value	Flare n= 8	No flare n= 65	p-value	Flare n= 9	No flare n= 66	p-value	Flare n= 15	No flare N=62	p-value
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												
Patient-reported 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
Patient-reported 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

Mean (SD) scores of patient-reported outcomes; TJC28, tender joint count in 28 joints; SJC28, swollen joint count in 28 joints; FLARE-RA, Flare Rheumatoid Arthritis questionnaire; RA-FQ, OMERACT (Outcome Measures in Rheumatology) Rheumatoid Arthritis Flare Questionnaire; *Based on the question "Are you experiencing a flare of your RA at this time" (yes/no).

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

Explanatory variables	Partly adjusted model**		Fully adjusted model**	
	OR (95% CI)	p-value	OR (95% CI)	p-value
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 five time points: baseline, month 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. OR, odds ratio; CI, Confidence Interval; EGA, evaluator global assessment; VAS, visual analogue 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 anti-rheumatic treatment by flare status

Escalation in anti-rheumatic treatment, n (%)	Month 6		Month 12	
	Flare, n=8	No flare n= 65	Flare n= 15	No flare n=62
	5 (63%)	5 (8%)	9 (60%)	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

bDMARD, biologic disease modifying antirheumatic drug; cDMARD, conventional disease modifying antirheumatic drug; MTX, methotrexate

* also change from oral to subcutaneous

** per oral, intra-muscular or intra-articular