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Cut-off value to identify a flare using the Flare Assessment in Rheumatoid Arthritis (FLARE-RA) questionnaire: analysis of the TOSCA study

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rheumatoid arthritis, self-assessment, flare, FLARE-RA questionnaire, patient reported outcome measure, disease activity

Abstract

Objective.

The Flare Assessment in RA (FLARE-RA) self-administered questionnaire aims to identify patients who had flare in the interval between two consultations. This study aimed to establish a threshold for FLARE-RA score to identify RA flare.

Methods.

The Tocilizumab SubCutAneous study evaluated the efficacy and safety of s.c. tocilizumab (TCZ) to patients with active RA. Disease activity was assessed with the DAS28ESR at baseline and at week 2 (W2), W4, W12 and W24. The FLARE-RA questionnaire was administered at W12 and W24. Patient satisfaction, assessed at baseline and W24 with the Patient Acceptable Symptom State (PASS), was used as a surrogate marker of no flare. A correlation was sought between the FLARE-RA score at W12 and W24 and the area under the receiver operating characteristic (ROC) curve (AUC) for monthly DAS28ESR. The optimal FLARE-RA cut-off below which patient satisfaction reached the PASS was explored with an ROC curve.

Results.

A total of 139 patients were included (mean age 57.3613.8 years, 74.1% women, mean RA duration 10.869.2 years, mean DAS28ESR 5.861.1). The correlation between the FLARE-RA score and DAS28ESR AUC was moderate at all times: $r = 0.41$ at W12 ($P < 0.0001$) and 0.51 at W24 ($P < 0.0001$). The optimal cut-off for the FLARE-RA score to identify absence of flare (i.e. an acceptable situation based on the PASS) was 2.3 with an AUC of 0.81.

Conclusion.

FLARE-RA and DAS28ESR assessment differ; we propose a FLARE-RA cut-off of 2.3, below which the situation (i.e. without flare) is acceptable for patients.

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Introduction

With the newest effective treatments that have improved the management of RA, sustained clinical remission or low disease activity are now considered achievable therapeutic targets [1, 2]. However, half of the patients in clinical remission experience temporary or prolonged worsening of their symptoms after 2 years of follow-up [3]. More specifically, RA evolution is not linear and has an inherent fluctuating disease course with a wide variation in severity. This clinical worsening, known as ‘flare’, was first defined in 2008 by the OMERACT 9 group as ‘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’ [4]. Other definitions of flares based on disease activity scores described and used in randomized controlled trials include an increase in DAS28 of >1.2 or >0.6 if the DAS28 is ≥ 3.2 [5].

Nevertheless, in daily practice, what patients consider ‘flare’ can vary in duration, intensity and frequency and can be transient, shorter, less severe or less frequent and not persistent or severe enough to be considered a flare by physicians. The ‘bad days’ still are an indication of fluctuating disease activity [3, 6]. In the Welsing et al. [7] study, these fluctuations in disease activity in patients with seemingly low DASs were found correlated with increased structural progression. Thus, RA flares deserve to be identified, even if not present at the time of the consultation, to prevent persistent remaining inflammatory activity that could be responsible for radiographic damage [3, 7, 8], functional impairment [8] and increased cardiovascular risk [9].

Even though consensual agreement on an ‘RA flare’ definition is still lacking, a novel patient-centred approach has emerged and focuses on the importance of the patient’s experience during flare to achieve a suboptimal control of the disease. A discordance exists between patients’ and physicians’ perceptions of flare as well as between patients [10, 11]. During flare, patients tend to prioritize general or emotional symptoms (fatigue, functional limitations, irritability, withdrawal, mood disturbances, etc.) over joint symptoms [10, 12].

Therefore, the Strategy of Treatment in Patients with Rheumatoid Arthritis working group has developed and validated the self-administered Flare Assessment in RA (FLARE-RA) questionnaire [12, 13]. The FLARE-RA score can be used to adequately assess the presence of a current and recent flare in the time interval between two visits to the rheumatologist or over the past 3 months. The FLARE-RA questionnaire includes 11 domains with two subscales: an arthritis-related subscale with five items (i.e. morning stiffness, night pain, swollen or tender joints, overall arthritis assessment and increased intake of analgesics) and a general symptom subscale with six items (i.e. fatigue, limitations, irritability, mood disturbances, withdrawal and need for help). Each item is graded by the patient on a numerical rating scale from 0 (completely untrue) to 10 (absolutely true). The overall FLARE-RA score is the mean of the 11 items, with a range from 0 (no flare) to 10 (maximum flare). This questionnaire has been cross-culturally adapted and validated in different languages including French, English, Spanish, Danish and Italian [12–17]. Disease activity is routinely assessed at the time of the clinic visits, but this tool aims to detect patients with fluctuating disease activity outside of consultations, the capture of such information being a key component in an adequate therapeutic decision-making.

Here, we present data from the phase IV study Tocilizumab SubCutaneous (TOSCA) aiming to (i) identify to what extent disease activity and flare overlap and (ii) establish a cut-off for

the FLARE-RA score to identify a score below which the situation (i.e. without flare) is acceptable for the patient.

Materials and methods

Study design and patient population

This is a sub-analysis of the TOSCA study, a national multicentre open-label single-arm phase IV trial, a component of the international TOZURA MA28557 Umbrella Program (ClinicalTrials.gov: NCT02001987 [18]). Briefly, this study aimed to evaluate the efficacy and safety of s.c. tocilizumab (TCZ) at a dose of 162mg administered once a week subcutaneously. TCZ s.c. was given either as monotherapy or combined with MTX or other nonbiologic DMARDs and with treatment duration of 24weeks. The population was patients with moderate to severe active RA with inadequate clinical response to conventional synthetic DMARDs (csDMARDs) and/or biologic DMARDs (bDMARDs), either TNF-blocker and/or abatacept. All patients were followed over a 6-month core period.

Patients

The study population included adults (≥ 18 years old) with active RA according to the revised ACR criteria (1987) [19] or EULAR/ACR (2010) criteria [20] and who had moderate-to-severe disease activity. CsDMARDs, oral low-dose corticosteroids (≤ 10 mg/day prednisone or equivalent), and NSAIDs; up to the maximum recommended dose were allowed if patients were on a stable dose regimen for at least 4weeks prior to the baseline visit. We excluded pregnant women and patients with severe ongoing infection, hypersensitivity to the active substance or any of the recipients, other autoimmune or concomitant serious diseases or laboratory abnormalities. The study was approved by the Ile de France VI Pitié- Salpêtrière Hospital Group review board and ethics committee and conducted according to the principle of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

Data collection for the TOSCA study

Disease activity, physical function and physician disease assessment were measured by the DAS28 with ESR (DAS28ESR), the HAQ Disability Index (HAQ-DI) and physician global assessment visual analogue scale (PGA-VAS). Patients attended visits at week 1 (W1; baseline), W2, W4, W12 and W24 and completed at each visit the DAS28ESR, HAQ-DI and PGA-VAS. The assessment of RA flare or disease activity fluctuations was based on the FLARE-RA questionnaire completed at weeks W1, W12 and W24. The Patient Acceptable Symptom State (PASS) [21, 22] assessment was completed at W1 and W24. The PASS consisted of answering ‘yes’ or ‘no’ to the question: ‘Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?’.

Study endpoints

The study had two main objectives. The first was to define the correlation between the FLARE-RA score at W12 and W24 and the DAS28ESR assessed over the 12 weeks preceding the FLARE-RA questionnaire assessment. The second was to determine a cut-off value for the FLARE-RA score and its subscales corresponding to an acceptable symptom

state for patients with RA. The determination of the cut-offs was addressed with the PASS, which was used to indicate a situation in which the patient had no flare since the last visit.

Statistical methods

Quantitative variables are expressed with mean (S.D.) and categorical variables with numbers (percentages). To assess the ability of the FLARE-RA questionnaire to detect relapse, we used correlation with the Spearman method between the RA-FLARE score at W12 and W24 and the area under the receiver operating characteristic (ROC) curve (AUC) for RA activity repeatedly measured by the physician (DAS28ESR). Univariate and multivariate repeated-measures analysis were used to determine the factors (age, sex, HAQ-DI, DAS28ESR, PGA-VAS) that could affect the FLARE-RA scores, estimating odds ratios (ORs) and 95% CIs.

In addition, the optimal FLARE-RA cut-off for patient health satisfaction as expressed by the PASS was explored by an ROC curve, which plots the probability of detecting a true signal (sensitivity) and false signal ($1 - \text{specificity}$). Detection of the optimal cut-off for the FLARE-RA score involved determining the point on the ROC curve with the minimum distance from the left upper corner of the unit square that corresponds to the point (0,1) at which sensitivity is equal to specificity (Sp) (a perfect test). Another approach to test the validity of an optimal cut-off value involved the Youden index method ($Se + Sp - 1$), whereby the optimal cut-off value corresponds to the point on the ROC curve with the highest vertical distance from the 45° diagonal line (ROC of an uninformative or non-discriminative test).

The overall accuracy to discriminate a flare with the FLARE-RA score is given by the area under the ROC curve (AUC). The AUC ranges from 0 to 1 (0¼perfectly inaccurate test; 1¼perfectly accurate test) and provides a measure of the model's ability to predict the outcome, the flare. An AUC of 0.5 indicates no discrimination (i.e. ability to diagnose patients with flare based on the test) and 0.7–0.8 is considered acceptable, 0.8–0.9 excellent and >0.9 outstanding [23].

All statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

We enrolled 183 patients with a diagnosis of RA in the TOSCA study in 29 hospital centres in France; 139 received TCZ s.c. and were included in the analysis (44 were excluded because of screening failure). The main demographic and clinical characteristics of patients are in [Table 1](#). The mean (S.D.) age of the patients was 57.3 (13.8) years, 74.1% were females and the mean disease duration was 10.8 (9.2) years. Overall, 85.5% of patients were seropositive (RF- and/or ACPA-positive), 65.6% had evidence of erosive disease with a mean DAS28ESR at baseline of 5.8 (1.1). In total, 52.5% (n¼473) of patients showed failure of a previous biological DMARD. TCZ s.c. was given as monotherapy in 30.9% (n¼443) of patients or combined with a csDMARD in 69.1% (n¼496), of whom 75% (n¼472) received MTX. Mean (S.D.) DAS28ESR decreased from 5.80 (1.14) at baseline to 4.47 (1.41) at W2, 3.56 (1.28) at W4, 2.71 (1.31) at W12 and then stayed stable till W24.

Mean (S.D.) FLARE-RA score decreased from 5.6 (2.8) at inclusion to 2.1 (2.2) at W12, then remained stable till W24 ([Fig. 1A](#)).

In the univariate repeated-measures model, FLARERA score was significantly correlated with DAS28ESR ($P < 0.001$), PGA-VAS ($P < 0.001$) and HAQ-DI total score ($P < 0.001$). FLARE-RA score was also significantly correlated with the PASS ($P < 0.001$) at baseline and W24. On univariate logistic regression analysis, at W24, improvement in physical function (HAQ-DI score ≤ 1) was associated with decreased DAS28ESR (OR ¼0.41, 95% CI: 0.27, 0.62; $P < 0.001$) and FLARE-RA score (OR ¼0.58, 95% CI: 0.45, 0.73; $P < 0.001$).

However, we found a moderate correlation between mean DAS28ESR AUC and FLARE-RA score. The Rho correlation coefficient was 0.41 (95% CI: 0.24, 0.55) at W12 ($P < 0.0001$) and 0.51 (95% CI: 0.36, 0.64) at W24 ($P < 0.0001$). On multivariate analysis, FLARE-RA score was associated with PGA-VAS (P ¼0.003), HAQ-DI ($P < 0.001$), DAS28ESR ($P < 0.001$) and age (P ¼ 0.001). FLARE-RA evolution stratified on PASS status at W24 is presented in [Fig. 1B](#). After 24 weeks on TCZ treatment, patients reported a FLARE-RA score of 1.4 to feel in an acceptable status of their disease and a score of 4.6, higher than initially, to feel in an unacceptable state.

From the ROC analysis, the optimal cut-off value for the global FLARE-RA score was 2.3, with sensitivity and specificity of 81.1% and 69.2%, respectively ([Table 2](#)). This score corresponded to a significant AUC of 0.81 (95% CI: 0.70, 0.91) ([Fig. 2](#)) to discriminate an acceptable and unacceptable PASS state at W24. The cut-off for the arthritis subscale was 1.8 with sensitivity and specificity of 79.7 and 80.8%, respectively, and corresponding to a statistically significant AUC of 0.81 (95% CI: 0.70, 0.92). For the FLARE-RA general symptoms subscale, the cut-off was 3.8 with sensitivity and specificity of 91.9 and 57.7%, respectively, and corresponding to a statistically significant AUC of 0.80 (95% CI: 0.70, 0.91).

Discussion

Flare is an important topic in the care of RA patients [24]. In the present study, we determined the cut-off FLARE-RA score to define a patient ‘in flare’ or ‘not in flare’. Patients with score under the 2.3 threshold for the FLARE-RA global score were considered ‘not in flare’ and at an acceptable symptom state, with acceptable-toexcellent discrimination by using ROC curves. Our previous report showed evidence of content validity, reliability, construct validity, and feasibility for the FLARE-RA questionnaire [13]. The strength of the FLARE-RA questionnaire remains its ability to detect a worsening of RA symptoms (arthritis and general symptoms) over the time interval between two visits to the rheumatologist and to capture it from both the patient’s and physician’s perspective, thus enabling the identification of suboptimal RA control [13].

The OMERACT 11 recommended core set domains for identifying and measuring RA flare, consisting of nine domains (pain, function, tender joints, swollen joints, patient global condition, fatigue, stiffness, participation and self-management) [24]. However, in clinical practice, we have no gold standard for assessing flare, and available instruments and thresholds have not yet reached consensus. Although several self-administered questionnaires have been developed to assess RA disease activity [25–28], the unique aim of the FLARE-RA questionnaire was to identify patients with flare or fluctuating disease activity in the time preceding the consultation and not just at the time of the visit. Other tools, such as the RA Flare Questionnaire (RA-FQ) [25], developed by the OMERACT RA flare group, evaluate patient-reported outcomes (PROs; pain, physical activity, fatigue, stiffness, daily activities) that have occurred during the week before the clinical visit, whereas the FLARE-RA questionnaire reveals exacerbations of RA symptoms over the past 3 months or since the last

visit. Similar to the RA-FQ, the Routine Assessment of Patient Index Data (RAPID3) [29], the RA Disease Activity Index (RADAI) and adapted RADAI-5 [30, 31], Patients' Activity Scale (PAS) or PAS-II [32], and PRO-CLinical Arthritis Activity questionnaire (PRO-CLARA) [33] are self-reported questionnaires, but they cover the PROs that occurred in <1 week as well.

TABLE 1 Demographic and clinical characteristics at baseline in the TOSCA study population ($n = 139$)

Age, mean (s.d.), years	57.3 ± 13.8
Female, n (%)	103 (74.1)
RA duration, mean (s.d.), years	10.8 ± 9.2
≥1 comorbidity (past or present), n (%)	128 (92.1)
RF- and/or ACPA-positive, n (%)	112 (85.5)
Erosive disease (i.e. ≥1 erosions on X-rays), n (%)	84 (65.6)
FLARE-RA score (0–10), mean (s.d.)	5.6 ± 2.8
DAS28 _{ESR} (2–10), mean (s.d.)	5.8 ± 1.1
HAQ-DI (0–3), mean (s.d.)	1.6 ± 0.7
PGA-VAS (0–100), mean (s.d.)	62.1 ± 17.7
Previous bDMARD failure, n (%)	73 (52.5)
Study treatment, n (%)	
Tocilizumab monotherapy	43 (30.9)
Tocilizumab combined with csDMARD	96 (69.1)
Tocilizumab + MTX	72 (75)
Tocilizumab + another csDMARD	24 (25)

bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; FLARE-RA: Flare Assessment in Rheumatoid Arthritis questionnaire; PGA-VAS: physician global assessment visual analogue scale.

FIG. 1 Evolution of FLARE-RA score in the 6-month study (A) and stratified by Patient Acceptable Symptom State at week 24 (B)

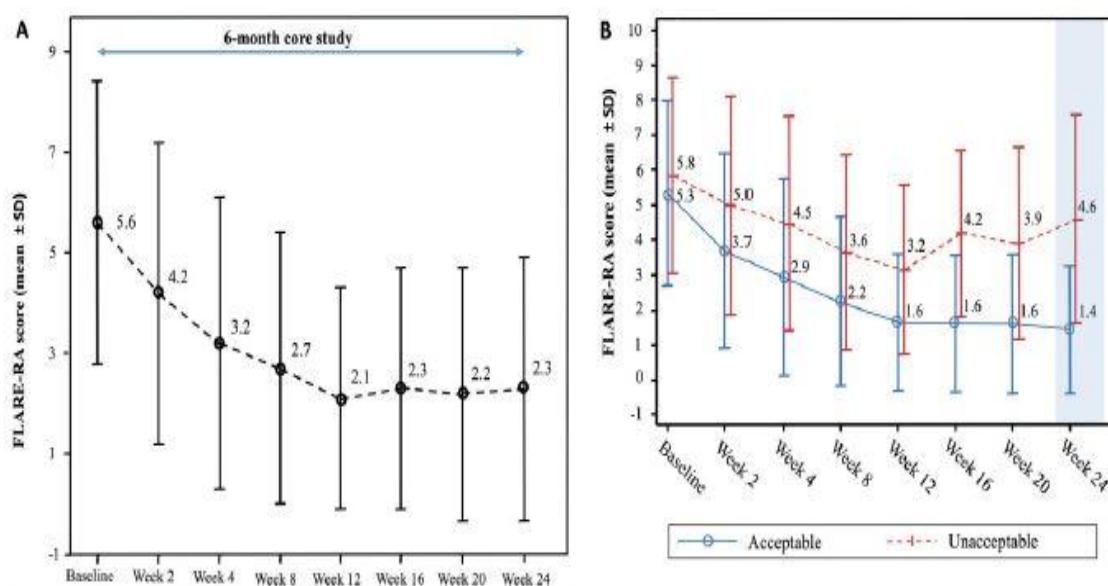
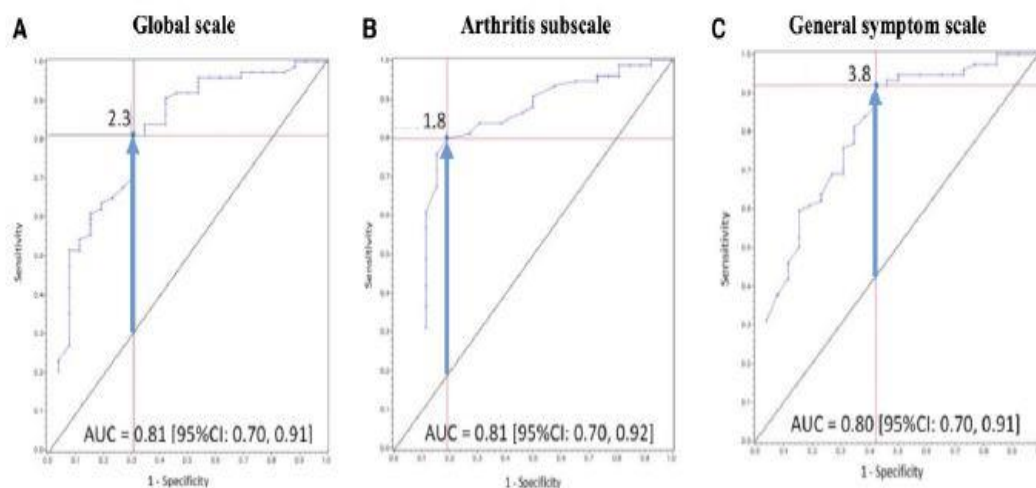


TABLE 2 Optimal cut-offs of the FLARE-RA score according to the Patient Acceptable Symptom State (PASS) at week 24 (W24)

W24 (n = 100)	Optimal cut-off ^a	AUC (95% CI)	Se%	Sp%
FLARE-RA score	2.3	0.81 (0.70, 0.91)	81.1	69.2
Arthritis subscale ^b	1.8	0.81 (0.70, 0.92)	79.7	80.8
General symptoms subscale ^c	3.8	0.80 (0.70, 0.90)	91.9	57.7

The cut-off corresponds to the optimal threshold for FLARE-RA score to discriminate individuals according to the PASS score at W24. ^aCut-offs were obtained according to the Youden index method. ^bMorning stiffness, night pain, joint swelling, joint pain, analgesics. ^cFatigue, limitations, irritability, mood disturbances, withdrawal, need for help. AUC: area under the receiver operating characteristic curve; FLARE-RA: Flare Assessment in RA questionnaire; Se: sensitivity; Sp: specificity.

FIG. 2 Receiver operating characteristic (ROC) curves for FLARE-RA questionnaire



ROC curves are shown with their respective area under ROC curve (AUC) values for the FLARE-RA global scale (A), arthritis subscale (B) and general symptoms subscale (C). An AUC of 0.5 indicates no discrimination and 0.7 to 0.8 is considered acceptable, 0.8–0.9 excellent and >0.9 outstanding. Vertical arrow: corresponding to the Youden index.

One of the key but yet unaddressed questions is the relevant threshold for RA flare detection. In the study of Myasoedova et al. [34], the optimal thresholds obtained on the global FLARE-RA scale were 1.82 and 2.18 for patients with disease duration between 2 and 5 years or >5 years, respectively. The anchor item used to determine these cut-offs was ‘the patient report of flare’. Higher FLARE-RA cut-offs to detect flare were noted with the other anchor items used (the DAS28–CRP >3.2 and change of treatment by the rheumatologist) [34].

Because a threshold to identify flare may differ to some extent depending on the chosen outcome, population and background and a binary classification system (‘in flare’ vs ‘not in flare’) may be more desirable for clinicians [35], we decided to determine the cut-offs for

the FLARE-RA according to a different anchor item than previously used. Thus, we used the PASS, a simple dichotomized PRO for the patient's satisfaction with their symptom state. The PASS reflects the overall level of well-being and is primarily defined as the highest level of symptom beyond which patients consider themselves well [21, 22, 36]. The concept of PASS is widely supported by the OMERACT [37] and constitutes a realistic target for disease management. Therefore, an important strength of our study is that this binary assessment of the patient satisfaction to discriminate thresholds of 'in flare' vs 'not in flare'.

An additional strength of this study is its ability to disentangle the two flare perspectives by two different cutoffs for the two subscales of the FLARE-RA score. We achieved acceptable-to-excellent discrimination for the threshold of 1.8 for the arthritis subscale and 3.8 for the general symptoms subscale. The general symptoms subscale focuses on subjective symptoms—somehow also poorly specific—that patients are likely to identify when a RA flare occurs, and the arthritis subscale relates to the disease clinical outcomes that are more easily understandable by and shareable with the physician. Both subscales are important to be evaluated in the treatment decision.

Overall, in our study, the FLARE-RA cut-off was lower for the arthritis than general symptoms subscale. The present observations differed from the Myasoedova et al. [34] study, in which general subscale cut-offs were all lower than those for the arthritis subscale, independent of the anchor item used. This observation could be explained by differing cultural behaviours and beliefs across continents and emphasizes the need to follow guidelines for translation and cross-cultural adaptations of the self-administered FLARE-RA questionnaire [38, 39].

Our study has several limitations. First, the global cutoff of 2.3 and the subscale cut-offs cannot be considered the threshold for warranting a change of treatment because we did not test this in our study. However, they can guide rheumatologists to recognize flare by taking into consideration the patient's perspective and decide on treatment change while relying on clinical judgement. Secondly, most patients included had long-standing disease, whose progression may differ from that for recently diagnosed RA patients. Thirdly, the patient's perception of the acceptability of the symptom state reflected by the PASS can be influenced by psychological and environmental factors unrelated to the disease and overestimate the FLARE-RA score. Finally, the FLARE-RA self-questionnaire does not include acute-phase reactant measures, CRP and ESR, as objective markers for inflammation and important predictors of later radiographic damage [5, 6, 40, 41]. However, data on acute-phase reactants are not frequently available in clinical practice; also, remission definitions (e.g. Clinical Disease Activity Index) not including acute-phase reactants perform similar to those including this parameter [42].

Disease activity measures such as the DAS28, the most widely used [43], are not quite adequate to determine flares in RA, and fluctuations in disease activity may lead to radiologic progression [7]. In this longitudinal study, we found a moderate correlation between DAS28ESR and FLARE-RA score, which indicates that data on flare can be missed when using only DAS28ESR. Although not widely used, our study shows the utility of PASS as an outcome criterion for unacceptable disease activity in RA, i.e. a flare that requires treatment adaptation. Future long-term longitudinal studies are needed to explore the added value of FLARE-RA over DAS28 or other disease activity measures.

Altogether, our study advocates a simple dichotomized FLARE-RA cut-off using PASS that can be easily used in clinical practice to help rheumatologists recognize a disease flare at the time of the visit and most importantly between two visits. The global threshold is particularly useful when there is doubt about the diagnosis of flare, and the subscale thresholds can guide physicians throughout the decision-making on treatment adjustments centred on the patient's well-being.

Conclusion

The patient's perspective of flare has an important impact on treatment decisions. We have identified a cutoff of 2.3 for the FLARE-RA score to help physicians detect a patient 'in flare' vs 'not in flare' over the past 3 months or since the last visit with the physician, particularly when the recognition of flare is uncertain. We also determined the cut-offs of 3.8 for the general symptoms subscale and 1.8 for the arthritis subscale for deciding on disease management.

A new combined flare measure (FLARE-RA score and increase in DAS28) may seem advantageous in managing RA and warrant the importance of the patient centred-approach. Further multinational studies are needed for the implementation of this tool in clinical practice and to recognize whether the use of FLARE-RA cut-offs may prevent or inhibit structural damage and functional disability in patients with RA.

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Data availability statement

The data underlying this article were provided by Roche-Chugai pharmaceuticals under permission and cannot be shared publicly. Data will be shared on reasonable request to the corresponding author with permission of Roche-Chugai pharmaceuticals.

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