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Evaluation and Validation of a Patient-completed Psoriatic Arthritis Flare Questionnaire

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ABSTRACT. ***Objective.*** Evaluation of a psoriatic arthritis (PsA), multidimensional, patient-completed disease flare questionnaire (FLARE).

Methods. The FLARE questionnaire was administered to 139 patients in a prospective observational study. The "gold standard" of flare was based on patient opinion. Test-retest reliability was evaluated by intraclass correlation coefficient (ICC). Disease activity was measured by the Psoriatic Arthritis Disease Activity Score (PASDAS), Group for Research and Assessment of Psoriasis and PsA (GRAPPA) Composite Exercise (GRACE), Composite Psoriatic Disease Activity Index (CPDAI), and Disease Activity Index for Psoriatic Arthritis (DAPSA).

Results. The most common symptoms of a PsA flare were musculoskeletal, followed by fatigue, frustration, loss of function, and an increase in cutaneous symptoms. The test-retest ICC for the FLARE questionnaire was 0.87 (95% CI 0.72–0.94). The optimum cut-off to identify a flare of disease was 4/10 (sensitivity 0.82, specificity 0.76; area under the curve 0.85). For those patients scoring ≥ 4, the mean score for the composite measures was as follows (score for those not reporting a flare in parentheses): PASDAS 5.3 ± 1.3 (3.1 ± 1.6); GRACE 4.5 ± 1.2 (2.2 ± 1.4); CPDAI 8.9 ± 2.5 (4.7 ± 3.1); and DAPSA 38.2 ± 20.3 (16.8 ± 14.9). In a new flare, the increase in composite measure score was calculated as follows: 1 for PASDAS and GRACE, 2 for CPDAI, and 7 for DAPSA. Agreement between the definition of flare using the cut-off of 4 from the questionnaire, and that indicated by the subject in a separate, standalone question was 0.57 (Cohen κ).

Conclusion. A PsA flare displays escalation of symptoms and signs across multiple domains. The FLARE questionnaire has external validity in terms of both composite disease activity and overall patient opinion about the state of their condition.

Key Indexing Terms: outcome measures, psoriasis, psoriatic arthritis

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Psoriatic arthritis (PsA) is a complex heterogeneous disorder with clinical manifestations in multiple areas, including joints, entheses, soft tissues and tendons, spine, and skin. Other clinical associations include metabolic syndrome, enhanced cardiovascular risk, eye and gut inflammation, and depression. A simple disease activity measure for such a complex disease has been a challenge to develop, and multiple measures are available. At the recent Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting (July 2020), the group voted to recommend the Psoriatic Arthritis Disease Activity Score (PASDAS) as a continuous measure and the minimal disease activity criteria as a target, for use in clinical trials.[1]

In rheumatoid arthritis, a working definition of *flare* includes the following statement: "Flare is any worsening of disease activity that would, if persistent, in most cases lead to initiation or change of therapy; and a flare represents a cluster of symptoms of sufficient duration and intensity to require initiation, change, or increase in therapy."[2] As might be expected with such a complex disease as PsA, the concept of a disease flare has been equally challenging. Qualitative work with patients revealed that the breadth of symptoms manifest during a flare of disease included not only cutaneous and musculoskeletal symptoms, but other symptoms such as fatigue, functional disability, and

emotional impact.[3] Further development of the concept of flare in PsA included tabulating, and subsequently shortening, the list of items used to describe it in a consensus exercise with patients and clinicians.[4] Using descriptions across the domains described by patients, and after reduction in the number of items using an online Delphi technique, a 10-item multidimensional, patient-completed disease flare questionnaire (FLARE) was subsequently developed for use in routine clinic appointments.[5] The questionnaire has items relating to symptoms in several domains, including joints, skin, function, fatigue, and emotions (see Supplementary Data, available with the online version of this article, for the full questionnaire).

The aim of the current study was to further examine and validate the FLARE questionnaire in a prospective longitudinal study undertaken in an outpatient setting in the United Kingdom. Validation involved comparison to patient opinion of flare, composite measures of disease activity (construct validity), test-retest reliability (reliability), and the development of thresholds of change for the composite measures equivalent to a flare of disease, according to the FLARE instrument.

METHODS

The ASSESSment of modified composite disease measures in recently diagnosed psoriatic arthritis (ASSESS) study was a prospective, longitudinal observational study undertaken in a routine outpatient setting in several centers in the UK (see Supplementary Figure 1, available with the online version of this article, for study flow chart). Full ethical approval was obtained from the North East York Research Ethics Committee (17/NE/0084). All participants gave informed written consent. Subjects were recruited consecutively; inclusion criteria were a fulfillment of the Classification Criteria for Psoriatic Arthritis and an ability to complete, in English, several patient-reported outcomes. Data were collected at baseline, 3 months, and 6 months. To evaluate test-retest reliability, a small cohort were asked to return within 2 weeks of their scheduled visit for a repeat of the measures used.

Composite outcome measures assessed. The PASDAS is a weighted index comprising assessments of joints, acute-phase response, enthesitis, dactylitis, physical function summary component of the 36-item Short Form Health Survey (SF-36), and patient and physician global scores.[6] The score range of the PASDAS is 0–10, with worse disease activity represented by higher scores. The GRAPPA Composite Exercise (GRACE) index is a composite score comprising assessments of joints, skin, function, and health-related quality of life (HRQOL), with each domain based on desirability functions that are ultimately combined into a single scale with a score range of 0–10 (worse disease activity is represented by higher scores).[6] The Composite Psoriatic Disease Activity Index (CPDAI) measures disease activity in 5 domains: peripheral joints, skin, enthesitis, dactylitis, and spine.[7] Within each domain, severity is graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe), according to predefined cut-offs. The score range is 0–15, with 15 representing worse disease activity. The Disease Activity Index for Psoriatic Arthritis (DAPSA) measures disease activity in peripheral arthritis, patient global visual analog scores (VAS), patient pain VAS, and C-reactive protein. The composite score is a simple sum of the scores, with higher scores representing worse disease activity.[8]

The FLARE instrument (Supplementary Data, available with the online version of this article) was developed after focused patient interviews and a Delphi process with members of GRAPPA and patient organizations in the UK. It is a 10-item self-completed questionnaire with questions covering several domains including skin, joints, participation, fatigue, and emotions.[3,5] The questions are answered by a simple yes/no so that the maximum score for the questionnaire is 10. Subjects were also asked to state, in a yes/no format, if they thought they were having a flare of their disease and, if they answered yes, to give an estimate of the duration of the flare.

Statistical methods. The sample size calculation for the ASSESS study was based on data from the GRACE study[6] and on a comparison of the psychometric performance of the original and modified GRAPPA composite indices. A total of 128 patients enabled a comparison of the scales, assuming that the limits of a 2-sided 90% CI excluded a difference in means > 0.8 (the minimally important difference of the GRAPPA composite index from the GRACE study).

Subjects self-reporting a flare were compared to those who did not report a flare. As many subjects reported having a flare at multiple visits, only data from the first occasion where a flare was reported were used. In these subjects, individual items of the FLARE questionnaire were examined by frequency, and, using receiver-operating characteristic (ROC) curve analysis, a cut-off score equivalent to a disease flare was identified. Test-retest reliability was examined with the intraclass correlation coefficient (ICC; using a mixed model, average measures approach). To determine the magnitude of change (increase) in score of each composite measure during a flare, only subjects declaring a flare after the baseline visit were used, as only these subjects had preceding clinical and patient-reported data values. For this estimate we calculated the increase by 3 different methods and rounded the mean to the nearest whole number. All procedures were performed in SPSS v25 (IBM Corp.).

RESULTS

One hundred thirty-nine subjects were recruited (59 male, 80 female, mean age 52.7 [SD 19–83] yrs, mean duration of psoriasis 21.9 [2–71] yrs, mean PsA duration 6.1 [range 0–41] yrs). In total, a flare of disease (patient-reported) occurred at 168 visits. At baseline, 69 patients self-reported a flare; at subsequent visits, in those patients not previously reporting a flare, a disease flare was reported by 31 patients. Thus, 100 patients were identified as having a new flare. Of these, 73 had further flares. None of the other 39 subjects reported having a flare of their disease.

Table 1 gives the frequency of individual item responses to the FLARE questionnaire. For those self-reporting a flare, the duration of the flare was indicated as < 1 week in 4%, 1–2 weeks

Table 1. FLARE item response for those reporting a flare vs not reporting a flare (single-item response).

Item	Reports Having a Flare, n = 100	Reports Not Having a Flare, n = 39
Worsening itch	49 (49)	10 (26)
Worsening skin area	42 (42)	12 (31)
Increasing joint pain	73 (73)	14 (36)
Increasing number of tender joints	55 (55)	8 (21)
Decrease in ability to perform activities	35 (35)	4 (10)
Worsening in ability to move easily	47 (47)	9 (23)
Increase in frustration	57 (57)	10 (26)
Worsening in depression	37 (37)	5 (13)
Worsening in feeling of tiredness all the time	61 (61)	13 (33)
Worsening in the number or combination of symptoms from your disease	48 (48)	10 (26)

Values are expressed as n (%). FLARE: psoriatic arthritis, multidimensional, patient-completed disease flare questionnaire.

in 14%, 2–4 weeks in 28%, 4–12 weeks in 33%, and > 12 weeks in 15%.

Test-retest data were available for 28 subjects. The mean FLARE score at baseline and 1 week later were 2.6 and 2.4, respectively. The ICC was 0.87 (95% CI 0.72–0.94). Cronbach α for the 10 items of the FLARE questionnaire was 0.85.

Using ROC curve analysis, and the self-reported question as the anchor, the optimal cut-off for the FLARE questionnaire, using Youden index, was calculated as a score of ≥ 4 (area under the curve 0.85, sensitivity 0.82, specificity 0.76). For those patients scoring ≥ 4 compared to those scoring < 4, the mean age was 50.0 (SD 13.5) years vs 54.7 (SD 11.1) years; the mean duration of disease was 2.5 (SD 4.8) years vs 5.2 (SD 6.7) years; and the percentage of males was 35% vs 58%. For those who scored > 4, the mean score for the composite measures was as follows (in parentheses, mean ± SD of score for those scoring < 4): PASDAS, 5.3 ± 1.3 (3.1 ± 1.6); GRACE, 4.5 ± 1.2 (2.2 ± 1.4); CPDAI, 8.9 ± 2.5 (4.7 ± 3.1); DAPSA, 38.2 ± 20.3 (16.8 ± 14.9). Agreement between the definition of flare using the cut-off of 4 from the questionnaire, and that indicated by the subject in a separate, standalone question was 0.57 (Cohen κ).

For the magnitude of change for each composite in those subjects who had a flare (patient self-report), 3 different estimates were obtained: the mean value of the composite in those who had a flare, the 50th centile of the distribution of scores, and the point on the ROC curve best fulfilling the Youden index (Table 2). The equivalent values for a flare were then calculated as 1 for the PASDAS and GRACE measures, 2 for the CPDAI, and 7 for the DAPSA.

In order to further examine external (construct) validity, score values for patient-reported outcomes were compared for those patients deemed to be flaring, using the cut-off of 4 from the FLARE questionnaire (Table 3). Significant differences were found for HRQOL measures (SF-36, Dermatology Life Quality Index, EuroQol 5-dimension scale, Psoriatic Arthritis Quality of Life), function (Health Assessment Questionnaire), disease impact (Psoriatic Arthritis Impact of Disease [PsAID]), and disease activity (Bath Ankylosing Spondylitis Disease Activity Index).

Table 2. The magnitude of change in score equivalent to a flare. There are 3 different estimates for each composite measure.

	Mean	50th Centile	ROC (Youden)
PASDAS	1.02	0.97	0.98
CPDAI	1.67	1	2
GRACE	1.09	0.88	0.97
DAPSA	7.7	9.2	4.4

CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity Index for Psoriatic Arthritis; GRACE: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Composite Exercise; PASDAS: Psoriatic Arthritis Disease Activity Score; ROC: receiver-operating characteristic.

Table 3. Scores on PROs according to FLARE instrument status (score ≥ 4).

PRO (range)	Those Not Having a Flare	Those Having a Flare
SF-36 PCS (0–100)	44.2 (11.0)	32.7 (9.9)
SF-36 MCS (0–100)	52.0 (9.4)	42.8 (11.9)
HAQ (0–3)	0.4 (0.6)	1.0 (0.7)
DLQI (0–32)	1.7 (2.6)	4.5 (5.6)
PsAID (0–10)	2.2 (2.0)	5.3 (1.8)
BASDAI (0–10)	2.8 (1.8)	5.9 (1.8)
PsAQoL (0–22)	4.4 (5.0)	10.3 (5.3)
EQ-5D (−0.28 to 1.00)	0.8 (0.2)	0.6 (0.2)

For each PRO, the contrast in score between "no flare" and "flare" was highly significant by both parametric and nonparametric tests. All values are expressed as mean (SD). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DLQI: Dermatology Life Quality Index; EQ-5D: EuroQol 5-dimension scale; FLARE: psoriatic arthritis, multidimensional, patient-completed disease flare questionnaire; HAQ: Health Assessment Questionnaire; MCS: mental component summary score; PCS: physical component summary score; PRO: patient-reported outcome; PsAID: Psoriatic Arthritis Impact of Disease questionnaire; PsAQoL: Psoriatic Arthritis Quality of Life questionnaire; SF-36: 36-item Short Form Health Survey.

DISCUSSION

This study represents further validation of the FLARE questionnaire and explores item-by-item change in subjects having a flare, as well as the relationship between the condition of "flare" with several composite measures of disease activity and patient-reported outcomes.

Unsurprisingly, in a rheumatology clinic setting, the items most frequently affirmed in those having a flare were pain and fatigue. These were also the top 2 items reported by patients ranking the impact of their disease in the development of the PsAID questionnaire.[9] However, emotional items such as an increase in frustration also ranked highly, with cutaneous items being reported by approximately half the subjects. Clearly, a flare can mean different things to different people, but the accumulation of symptoms indicated in this study is also important, with 4 or more items optimally representing the flare state experienced by the patient.

Of interest is the long duration of symptoms reported by patients in a flare, with almost 50% having symptoms of a flare for 4 weeks or more. In the post–coronavirus disease 2019 (COVID-19) era, the availability of a patient-completed disease flare questionnaire is of interest, with many clinic appointments being conducted remotely. Such an instrument might aid remote monitoring and help to identify those people who need a face-to-face appointment.

When a patient reports having a flare, it can mean several things. However, in using the FLARE questionnaire, with a cut-off of 4, we have shown that the definition of *flare* not only relates to several disease activity composite measures but also to HRQOL (both from a skin and musculoskeletal point of view) and disease impact across several domains of disease (as measured by the PsAID questionnaire). All of these relationships contribute to further validation of the FLARE questionnaire. However, this multidimensional flare questionnaire captures many more aspects of the disease, and its impact, than the existing composite measures. A flare of disease from a patient

point of view is more than just the joints, as previously indicated.[3] A simple composite measure that focuses on the articular aspect of the disease will not capture the spectrum of symptoms that comprise a flare of disease. The FLARE questionnaire enables the patient to tell the health professional more about the way their disease is making them feel, and goes beyond objective clinical data.

Previous work with the FLARE questionnaire in Italy also found that a score of ≥ 4 adequately identified subjects who thought they were having a flare, so there is consistency between countries in that respect.[10] Also concordant were the internal consistency, relationship to measures of disease activity, and test-retest reliability score, in addition to the agreement score between the questionnaire and patient opinion (0.57 and 0.54, respectively). It seems, therefore, that there is at least some cross-cultural validity with this instrument.

In conclusion, this study has further examined the validity of the multidimensional FLARE questionnaire, using data from routine clinical practice. The questionnaire was shown to be reliable and to have external validity. A score of ≥ 4 on the FLARE questionnaire is an appropriate cut-off, with acceptable sensitivity and specificity in patients who self-report a flare of their disease. Cut-offs for a number of composite measures, with an increase in score equivalent to a flare, have been estimated and may be of use in future studies.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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