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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 was evaluated by intra-class correlation coefficient (ICC). Disease activity was measured by the PASDAS, GRACE, CPDAI and 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 curve 0.85). For those patients scoring 4 or above, the mean score for the composite measures was as follows (score for those not reporting a flare in brackets): 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). In a new flare the increase in composite measure score was calculated as follows; 1 for PASDAS and GRACE, 2 for CPDAI, 7 for DAPSA. Moderate agreement was found between the definition of flare using the cut-off of 4, indicated by subjects in a separate question.

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

Introduction

Psoriatic arthritis 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 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 index (PASDAS) as a continuous measure, and the minimal disease activity criteria (MDA) as a target, for use in clinical trials (unpublished data).

In rheumatoid arthritis a working definition of a 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" (1). 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 the breadth of symptoms manifest during a flare of disease and included not only cutaneous and musculoskeletal symptoms but other symptoms such as fatigue, functional disability and emotional impact (2). Further development of the concept of flare in psoriatic arthritis included tabulating, and subsequently shortening, the list of items used to describe a flare in a consensus exercise with patients and clinicians (3). Using descriptions across the domains described by patients, and after reduction in the number of items using an online Delphi technique, a 10 item FLARE questionnaire was subsequently developed for use in routine clinic

appointments (4). The questionnaire has items relating to symptoms in several domains, including joints, skin, function, fatigue and emotion (see online supplement for the full questionnaire).

The aim of the current study was further examination and validation of the FLARE questionnaire in a prospective longitudinal study undertaken in an out-patient setting in the UK. 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.

Materials and 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 out-patient setting in several centres in the UK (see on-line supplement for study flow chart). Full ethical approval was obtained from North East York Research Ethics Committee (17/NE/0084). All participant gave informed written consent. Subjects were recruited consecutively: inclusion criteria included a fulfilment of the CASPAR criteria for psoriatic arthritis and an ability to complete, in English, several patient-reported outcomes. Data were collected at baseline, 3 and 6 months. To evaluate test-retest 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 SF36, and patient and physician global scores(5). The score range of the PASDAS is 0–10, with worse disease activity represented by higher scores. The GRACE index is a composite score comprising

assessments of joints, skin, function and health-related QOL, with each domain based on desirability functions, which are ultimately combined into a single scale with a score range 0 – 10, with worse disease activity represented by higher scores (5). The CPDAI measures disease activity in 5 domains: peripheral joints, skin, enthesitis, dactylitis, and spine (6). Within each domain, severity is graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe), according to pre-defined cut-offs. The score range is 0 – 15 with 15 representing worse disease activity. The DAPSA measures disease activity in peripheral arthritis, patient global VAS, patient pain VAS, and CRP. The composite score is a simple sum of the scores, with higher scores representing worse disease activity.(7)

The FLARE instrument (see supplement) was developed after focussed patient interviews, and a DELPHI process with members of GRAPPA (Group for research and assessment of psoriasis and psoriatic arthritis)) and patient organisations in the UK. It is a 10 item self-completed questionnaire with questions covering several domains including skin, joints, participation, fatigue, and emotions (2, 4). 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 (5) and was based 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 two-sided 90% confidence interval excluded a difference in means of more than 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 ROC curve analysis, a cut-off score equivalent to a disease flare was identified. Test-retest was examined with the intra-class correlation coefficient (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 three different methods and rounded the mean to the nearest whole number. All procedures were performed in SPSS v 25.

Results

139 subjects were recruited (59 male, 80 female, mean (range) age 52.7 years (19 – 83y), mean (range) duration of psoriasis 21.9 years (2 – 71y), mean (range) duration of psoriatic arthritis 6.1 years (0 – 41y). In total, a flare of disease (patient reported) occurred at 168 visits. At baseline 69 patients self-reported a flare and, at subsequent visits, in those patients not previously reporting a flare, a flare of disease was reported by 31 patients, thus identifying 100 patients with 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 less than one week in 4%, 1-2 weeks in 14%, 2-4 weeks in 28%, 4-12 weeks in 33%, and more than 12 weeks in 15%.

Test-retest data were available for 28 subjects. The mean FLARE score at baseline and one week later were 2.6 and 2.4 respectively. The ICC was 0.87 (95% CI 0.72 -0.94). Cronbach's alpha 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's index, was calculated as a score of 4 or above (AUC 0.85, Sensitivity 0.82, specificity 0.76). For those patients scoring 4 or above, the mean age was 50.0y (sd 13.5y) compared to 54.7y (sd 11.1y) for those scoring less than 4; the mean duration of disease was 2.5y (sd 4.8y) compared to 5.2y (sd 6.7y) for those scoring less than 4; the percentage of males was 35% compared to 58% for those scoring less than 4. For those who scored 4 or above the mean score for the composite measures was as follows (in parentheses, mean ± sd of score for those scoring less than 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 and that indicated by the subject in a separate question was 0.57 (Cohen's kappa).

For the magnitude of change for each composite in those subjects who had a flare (patient self-reported) three different estimates were obtained: the mean value of the composite in those who had a flare, the 50^{th} centile of the distribution of scores, and the point on the ROC curve best fulfilling Youden's 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 health

related quality of life measures (SF36, DLQI, EQ5D, and PsAQoL), function (HAQ), disease impact (PsAID) and disease activity (BASDAI).

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' and 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 two top items reported by patients ranking the impact of their disease in the development of the psoriatic arthritis impact of disease questionnaire (8). However, emotional items such as an increase in frustration also ranked highly, with cutaneous items being reported by about 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-covid era, with many clinic appointments being conducted remotely, the availability of patient completed disease flare questionnaire is of interest: 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 but using the FLARE questionnaire, and using a cut-off of 4, we have shown that this relates to several disease activity composite measures, but also relates to health related quality of life (both from a skin and musculoskeletal point of view) and disease impact across several domains of disease measured by the PsAID questionnaire, all of which contribute to further validation

of this questionnaire.However, this multidimensional flare questionnaire captures much more than the existing composite measures, even the more complex (and less easy to calculate) measures. A flare of disease from a patient point of view is more than just the joints, as previously indicated (2). A simple composite measure that focusses on the articular aspect of the disease will not capture the spectrum of symptoms that comprise a flare of disease. This 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 or above adequately identified subjects who thought they were having a flare, so there is consistency between countries in that respect (9). Also consistent were the internal consistency, relationship to measures of disease activity, and test-retest reliability score, in addition to the agreement score between 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 have external validity. A score of 4 or more 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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References

1. 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.

2. Moverley A, Vinall-Collier KA, Helliwell PS. It's not just the joints, it's the whole thing: qualitative analysis of patients' experience of flare in psoriatic arthritis. Rheumatology (Oxford) 2015;54:1448-53.

3. Moverley AR, Waxman R, de Wit M, Parkinson A, Campbell W, Brooke M, et al. Development of a Flare Instrument for Use in Psoriatic Disease: A Report from the 2015 GRAPPA Annual Meeting. J Rheumatol 2016;43:974-8.

4. Helliwell P, FitzGerald O, Coates L, Callis Duffin K, Mease P. GRAPPA 2016 Project Report. J Rheumatol 2017;44:706–10.

5. Helliwell PS, FitzGerald O, Fransen J, Gladman DD, Kreuger GG, Callis-Duffin K, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis 2013;72:986-91.

6. Mumtaz A, Gallagher P, Kirby B, 3Waxman R, Coates LC, Veale JD, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis 2011;70:272-7.

7. Nell-Duxneuner VP, Stamm TA, Machold KP, Pflugbeil S, Aletaha D, Smolen JS. Evaluation of the appropriateness of composite disease activity measures for assessment of psoriatic arthritis. Ann Rheum Dis 2010;69:546-9.

8. Gossec L, de Wit M, Kiltz U, Braun J, Kalyoncu U, Scrivo R, et al. A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and

preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Ann Rheum Dis 2014;73:1012-9.

9. Scriffignano S, Perrotta FM, De Socio A, Altobelli A, Sessa P, Scrivo R, et al. Validation of the Italian version of proposed GRAPPA flare questionnaire for patients with psoriatic arthritis. Clin Exp Rheumatol 2019;37:193-198.

Supplementary material (on line)

ASSESS study flow chart

FLARE questionnaire