Validation of the Italian version of proposed GRAPPA flare questionnaire for patients with psoriatic arthritis

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Abstract

Objective

The aim of the present study was to validate an Italian version of the GRAPPA flare instrument to identify patients with psoriatic arthritis (PsA) with a possible disease flare.

Methods

This was a cross-sectional study enrolling consecutively PsA patients classified with CASPAR criteria. Inclusion criteria were: age ≥18 years and stable treatment (at least six months of follow-up) with conventional synthetic or biological DMARDs. The flare questionnaire was administered at baseline and within a two-week interval. Internal consistency of the questionnaire was evaluated with Cronbach's alpha coefficient. Construct validity of flare questionnaire was assessed using the correlation between flare score and disease activity indices, HAQ and serum C-reactive protein. Cohen's κ was performed to assess the agreement level between the patient's perception of flare and the score of the questionnaire. Finally, test-retest was performed to assess the reliability of the instrument.

Results

46 PsA patients were enrolled in this study. Of these, 30.4% reported a status of flare of their disease. The questionnaire was internally consistent (alpha=0.81). Moreover, the questionnaire score correlated with the main disease activity indices (Spearman Rho ranging from 0.30 to 0.66; p<0.01). The score of flare questionnaire showed a moderate agreement with the perception of flare from the patients (Cohen's κ=0.54). Test-retest reliability showed a good intra-class correlation.

Conclusion

This initial validation of the Italian version of the GRAPPA flare instrument was favourable. Our results confirm the utility of this questionnaire in the assessment of flare in PsA.

Key words
psoriatic arthritis, flare, disease activity, outcomes

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease that belongs to the group of spondyloarthritis (SpA). PsA affects about 1/3 of patients with psoriasis and clinical manifestation can be heterogeneous, with the involvement of different domains (joints, skin, enthesis and extra-articular manifestations) (1). In recent years, the available treatment strategies for PsA allowed a better control of all disease domains, with the possibility of achieving a state of remission or low disease activity, and the improvement of articular function and quality of life, even for a long-term follow-up (2-6). However, several factors can influence the response to treatment in PsA patients and, even those that achieve a status of remission or low disease activity, a disease flare can occur (7). Furthermore, the heterogeneity of the disease could lead to a flare in different domains. In fact, a patient could have a flare in a domain (for example skin) and remission in other domains (enthesis or joint). To our knowledge, the concept of flare in PsA still lacks an objective definition and no measures have been validated to assess this important aspect.

Recently the Group for Research and Assessment for Psoriasis and Psoriatic Arthritis (GRAPPA) developed a flare instrument based on patient's and physician's perspective that includes several disease domains centred on patient reported measures (8). The flare instrument has not been yet validated for its use in PsA, thus the aim of our study was to validate an Italian version of this GRAPPA flare instrument to identify, in clinical practice, PsA patients with a possible disease flare.

Materials and methods

Patients

This was a cross-sectional study involving two Italian Rheumatology Units.

Patients with PsA classified according to the Classification criteria for Psoriatic Arthritis (CASPAR) (9) were consecutively enrolled. Inclusion criteria was: age ≥18 years and stable treatment (at least six months of follow-up) with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or biological (b) DMARDs. For each patient, we collected demographic and clinical data (age, sex, disease's duration, treatment) and laboratory parameters (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]).

Furthermore, the following data were collected: number of swollen joints (out of a total of 66), number of tender joints (out of a total of 68), present or previous dactylitis, Psoriasis Area Severity Index (PASI) (10), Leeds Enthesitis index (LEI) (11), the Visual Analogue Scale (VAS) for pain, patient global assessment of disease activity (PtGA) on VAS, the physician global assessment of disease activity (VAS physician) (12) and the health assessment questionnaire (HAQ) (13). To evaluate disease activity, we used the Disease Activity Score for Psoriatic Arthritis (DAPSA) and its clinical variant (cDAPSA) (14). Minimal Disease Activity (MDA) status was defined according to Coates *et al*. (15); MDA 5/7 and DAPSA ≤14 were used to identify a status of minimal and low disease activity respectively, while DAPSA ≤4, and MDA 7/7 were used to identify a status of remission.

A condition of flare, from the patient's perspective was defined by using the final question of the instrument: "are you experiencing a flare of your disease in the last three months?" (yes/no response). The same day, the physician assessed the condition of the patient, namely flare yes or no.

All patients were invited to fill in the self-administered questionnaire and to return to the physician when it was completed.

Feasibility was also evaluated, measuring if the questionnaire was easy to perform and how long was necessary to complete.

All patients gave their written informed consent and the study protocol was approved by local committee (protocol n. 0001-09-2017). Consent was obtained according to the declaration of Helsinki with a pre-administered letter emphasising the anonymous and confidential nature of each question.

Flare questionnaire

The flare questionnaire consists of 12 questions: questions number 1 and 2

explore the skin domain; questions number 3, 4, 5 and 6 explore joint domain in terms of pain, number of joints involved and joint function; questions number 7, 8, 9 and 10, explore the psycho-somatic manifestations of the disease (8). We assigned a score of 1 for the response "yes" and 0 for the response "no". Hence, the total score ranged from 0 to 10.

The eleventh question assesses the patient' perception of the global disease status, and, finally, if the patients' status has deteriorated, the questionnaire asks the duration of this deteriorated status (Supplementary file).

Translation

An Italian Rheumatologist (E.L.) translated the questionnaire from English to Italian as a first draft; then he sent it to a mother tongue English speaker with a good knowledge of Italian but without any knowledge of either questionnaire (the original in English and the Italian version). The mother tongue English speaker back- translated the Italian version of the questionnaire and no significant cultural adaptations were made (Supplementary file).

Statistical analysis

Statistical analysis was performed using the SPSS package (v. 17) and GraphPad Prism 5. Normally distributed variables were summarised using mean ± standard deviation (SD) and non-normally distributed variables by median/25th-75th percentile. Percentages were used when appropriate. The significance of the correlation was assessed by the correlation coefficient of Spearman's rank. The concordance between the different indices used, was carried out through Cohen's test. Internal consistency was assessed with Cronbach's alpha coefficient. External validity and construct validity of the questionnaire was assessed by comparing the score of flare questionnaire with the 'gold standard' (composite disease activity indices, patient reported outcomes and function questionnaire-HAQ). The test-retest reliability was evaluated within a two-week interval between measurement points and was investigated by computing the intra class correlation. To identify the cut-off related to the flare questionnaire we used Receiver Operating Characteristics (ROC) curve, using as a gold standard of flare by using the physician's and patient's perspective. *p*-values less than 0.05 were considered significant. Sample size was not calculated since the design of the study that was conceived as a validation study.

Table I. Demographic and clinical features of enrolled PsA patients.

Age, mean (SD); years	55.7 (12.9)
Male/female	30/16
Disease duration, mean (SD); years	10.7 (8.2)
Treatment	
csDMARDS, n (%)	19 (41.3)
bDMARDs, n (%)	27 (58.7)
PASI	
Clear, n (%)	18 (39.1)
Almost clear, n (%)	16 (34.7)
Moderate, n (%)	8 (17.4)
Severe, n (%)	3 (6.52)
Very severe, n (%)	1 (2.1)
Extra-articular manifestations, n (%)	2 (4.34)
Dactylitis	
Previous / present, n (%)	9 (19.6)
Absent, n (%)	37 (80.4)
Swollen joints (median/25th-75th percentile)	0/0-1.25
Tender joints (median/25th-75th percentile)	1.5/0-6.25
LEI (median/25th-75th percentile)	0/0-1.25
PtGA (median/25th-75th percentile)	40/20-56.25
VAS physician (median/25th-75th percentile)	30/10-50
VAS pain (median/25th-75th percentile)	40/10-60
DAPSA (median/25th-75th percentile)	12.2/4.7-19.4
cDAPSA (median/25th-75th percentile)	12/ 4.75- 19
MDA 5/7 n (%)	19 (41.3)
MDA 7/7 n (%)	6 (13)
HAQ (median/25th-75th percentile)	0.375/0 - 0.75
ESR (median/25th-75th percentile)	10/ 6.5- 21
CRP, mg/dl (median/25th-75th percentile)	0.2/ 0.2- 0.4
"Flare" patient n (%)	14 (30.4)
"Flare" physician n (%)	13 (28.2)
"Flare" questionnaire score (median/25th-75th percentile)	3/1-5

csDMARDs: classic synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biologic disease-modifying anti-rheumatic drugs; PASI: psoriasis area severity index; LEI: Leeds enthesitis index; PtGA: patient's global assessment; VAS: visual analogue scale; DAPSA: disease activity score for psoriatic arthritis; cDAPSA: clinical disease activity score for psoriatic arthritis; MDA: minimal disease activity; HAQ: health assessment questionnaire; ESR erythrocyte sedimentation rate; CRP: C-reactive protein.

Table II. Correlations between flare score and disease activity indices, patient reported outcome and functional indices.

Variable	Sperman Rho	*p*-value
Age	0.17	0.25
Disease duration	-0.11	0.46
Tender joints	0.4	0.005
Swollen joints	0.38	0.0075
LEI	0.37	0.009
PtGA	0.54	<0.001
VAS physician on disease activity	0.53	<0.001
VAS pain	0.66	<0.001
DAPSA	0.6	<0.001
cDAPSA	0.61	<0.001
HAQ	0.47	<0.0001
PASI	0.28	0.13
CRP (mg/dl)	0.41	<0.004

LEI: Leeds enthesitis index; PtGA: patient's global assessment; VAS: visual analogue scale; DAPSA: disease activity score for psoriatic arthritis; cDAPSA: clinical disease activity score for psoriatic arthritis; HAQ: health assessment questionnaire; PASI: psoriasis area severity index; CRP: C-reactive protein.

Results

From January 2017 to December 2017, we enrolled 46 PsA patients that fulfilled the inclusion criteria.

Table I shows the main demographic and clinical features of the enrolled patients.

Mean age (SD) was 55.7 (12.9) years. Mean disease duration (SD) was 10.7 (8.2) years. Of the 46 PsA patients, 27 (58.7%) were in treatment with bDMARDs, while 19 (41.3%) with only csDMARDs.

MDA5/7 was found in 19 (41.3%) patients. Median (25^{th} -75^{th} percentile) DAPSA was 12.2 (4.7–19.4). About 54% of patients were in DAPSA low disease activity (defined as DAPSA score ≤14). Of the 46 PsA patients, 30.4% described a current status of flare of their disease based on the question on patient's perception. The median score for the flare questionnaire was 3.

The flare questionnaire showed a good internal consistency (Cronbach's alpha =0.81).

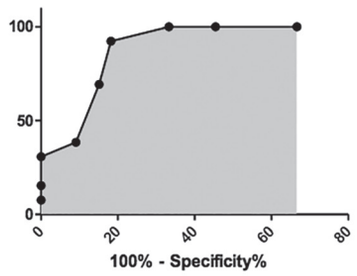
Table II shows the Spearman's Rho correlations between the score obtained by flare questionnaire and the main disease activity indices, functional score and patient reported outcomes. In particular, a good correlation (Rho ranging from 0.30 to 0.66; $p<0.01$) was found with: number of swollen and tender joints, LEI, PtGA, VAS physician, VAS pain, DAPSA, cDAPSA, HAQ, demonstrating the construct validity of the Italian version of flare questionnaire.

Of interest, no correlation was found between PASI score and flare questionnaire.

Test-retest reliability showed a good intra-class correlation - ICC (0.97; 95% confidence interval 0.94–0.98). Moreover, to identify a possible cut-off useful to discriminate a condition of flare, the ROC curves were peformed. Figure 1 shows the Area Under the Curve (AUC) of the questionnaire score in respect to physician's and patient's perception. A score = 4 had 92.3% sensitivity and 81.8% specificity with a likelihood ratio of 5.08 for the presence of disease flare evaluated by physician. When we compared the questionnaire to the patient's perception, sensitivity was 85.71 and specificity was 75.0, with a likelihood ratio of 3.43, by using the same cut-off. Cohen's kappa concordance between the absence of flare (using the cut-off of 4) and the presence of state of low disease activity (DAPSA ≤14) or MDA 5/7 showed a moderate agreement (κ= 0.41 and κ=0.50, respectively) (Table III). Finally, Cohen's kappa concordance between the score of flare questionnaire and the perception of flare, by using patients and physician's perspective showed a moderate agreement (κ=0.54 and 0.58, respectively).

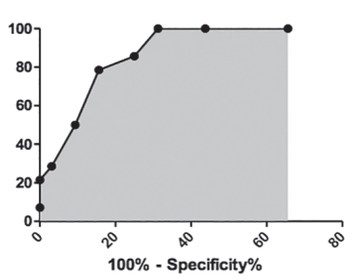
In terms of feasibility, patients filled in the questionnaire in about 5 minutes, and they reported that the questions were simple and easy to understand.

A



Flare score	Sensitivity%	95% CI	Specificity%	95% CI	Likelihood ratio
>0.5	100.0	75.29% to 100.0%	33.33	17.96% to 51.83%	1.50
>1.5	100.0	75.29% to 100.0%	54.55	36.35% to 71.89%	2.20
>2.5	100.0	75.29% to 100.0%	66.67	48.17% to 82.04%	3.00
>3.5	92.31	63.97% to 99.81%	81.82	64.54% to 93.02%	5.08
>4.5	69.23	38.57% to 90.91%	84.85	68.10% to 94.89%	4.57
>5.5	38.46	13.86% to 68.42%	90.91	75.67% to 98.08%	4.23
>6.5	30.77	9.092% to 61.43%	100.0	89.42% to 100.0%	-
>8	15.38	1.921% to 45.45%	100.0	89.42% to 100.0%	-
>8.5	7.692	0.1946% to 36.03%	100.0	89.42% to 100.0%	-

B



Flare score	Sensitivity%	95% CI	Specificity%	95% CI	Likelihood ratio
> 0.5	100.0	76.84% to 100.0%	34.38	18.57% to 53.19%	1.52
> 1.5	100.0	76.84% to 100.0%	56.25	37.66% to 73.64%	2.29
> 2.5	100.0	76.84% to 100.0%	68.75	49.99% to 83.88%	3.20
> 3.5	85.71	57.19% to 98.22%	75.00	56.59% to 88.54%	3.43
> 4.5	78.57	49.20% to 95.34%	84.38	67.21% to 94.72%	5.03
> 5.5	50.00	23.04% to 76.96%	90.63	74.98% to 98.02%	5.33
> 6.5	28.57	8.389% to 58.10%	96.88	83.78% to 99.92%	9.14
> 8.	21.43	4.658% to 50.80%	100.0	89.11% to 100.0%	-
> 9.5	7.143	0.1807% to 33.87%	100.0	89.11% to 100.0%	-

Fig. 1. Sensitivity, specificity, likelihood ratio and area under the curve (AUC) of the flare questionnaire in respect to physician's (A) and patient's (B) perspective of flare (assumed as gold standard to detect flare) in patients with PsA.

Discussion

In axial SpA, the Assessment in Spondyloarthritis International Society (ASAS) developed 12 preliminary definitions of 'flare' based on widely used

Table III. Agreement (Cohen's κ) between the patient's perspective of disease flare, physician's perspective of flare, DAPSA, LDA and MDA 5/7 in the enrolled patients.

	Flare (according to patient's perspective)
Flare (according to physician's perspective)	0.58
Flare (assessed by flare questionnaire score ≥4)	0.54
DAPSA LDA	0.41
MDA 5/7	0.5

DAPSA: disease activity score for psoriatic arthritis; LDA: low disease activity; MDA: minimal disease activity.

indices and different studies were performed on this topic (16, 17). On the other hand, at present in PsA patients this aspect still remains an important unmet need for an optimal management of this condition. In fact, several factors can influence response to treatment and long treatment regime (18) in PsA patients and, even in those who achieve a status of remission or low disease activity, a disease flare, described as a something beyond just the physical symptoms of disease, can still occur (19). Recently, in PsA, a systematic literature review found only 5 articles relating to flare (8) and most studies analysed the lost or the absence of a disease target, such as remission or low disease activity (20, 21). However, in a complex disease such as PsA, it could be difficult to identify a precise definition since there are different points of view in respect to what is a "flare" of disease and in which domain (20). Therefore, during a GRAPPA meeting, different items were selected as important, either by patients and physicians, and the consensus view concluded that the components of a flare instrument should be derived from patients' perspective to assess articular, skin, emotional, participation, and fatigue domains (20).

In our patients, by using the GRAPPA flare questionnaire, we observed a good correlation with HAQ and other disease activity indices, as well as inflammatory markers. The skin component, represented by PASI, did not show any significant correlation with the flare questionnaire. Despite questions assessing skin involvement in the questionnaire, it is probable that in a rheumatology setting, in which most of the patients had low PASI score, the presence of pain, joint involvement and functional disability could primarily influence the perception of flare by the patients.

Interestingly, as shown in Table II, the flare questionnaire did not correlate with age or disease duration indicating that the presence of disease flare is not linked to patient's age or long disease duration. In our study the flare instrument score was compared with two gold standards, namely the patient's and physician's perception of disease flare. As shown in figure 1, ROC analysis demonstrated a good sensitivity and specificity for values = 4. The agreement in the assessment of flare between the questionnaire and both physician's and patient's perception was moderate (κ=0.54 and 0.58 respectively), showing that sometimes a discrepancy between patients and physicians may be found. Indeed, this result might be related to the construction of the instrument, able to identify a flare that is beyond the patient's and physician's perception when compared.

Finally, the Italian version of the flare instrument did not require any major cultural adaptation in the translation process and in many cases a simple literal translation was necessary. It was easy to understand by the patients and quick to complete. In fact, many questions, such as those about the presence of an increase in the number or swollen joints, were found very appropriate by the patients, reflecting the potential increase in disease activity related to a real flare of the disease. Our results show that the Italian version of flare instrument is a valid instrument to measure flare in the different disease domains of PsA, even when translated.

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