PHYSICIAN GLOBAL ASSESSMENT (PhysGA) IN PSORIATIC ARTHRITIS (PsA). A MULTICENTRE GRAPPA STUDY.

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ABSTRACT

Objective. Physician Global Assessment (PhysGA) of disease activity is a major determinant of therapeutic decision-making. This study assesses the reliability of the PhysGA, measured by means of 0-100 mm visual analogue scale (VAS), and the additional utility of separate VAS scales for musculoskeletal (PhysMSK) and dermatologic manifestations (PhysSk) in Psoriatic Arthritis (PsA) patients.

Methods. 16 centres from eight countries enrolled 319 consecutive PsA patients with PsA. PhysGA, PhysMSK and PhysSk evaluation forms were administered at enrolment (W0) and after one week (W1). Detailed clinical data regarding musculoskeletal manifestations, as well as dermatological assessment, were recorded.

Results. Comparison of W0 and W1 scores showed no significant variation (intraclass correlation coefficients for PhysGA was 0.87, PhysMSK 0.86, PhysSk 0.78) demonstrating the reliability of the instrument. PhysGA scores were dependent on PhysMSK and PhysSk ($p<0.0001$) with a major impact of the MSK component (B=0.69) compared to skin (B=0.32). PhysMSK was correlated with the number of swollen, tender

joints and presence of dactylitis (p<0.0001). PhysSk scores were correlated with the extent of skin psoriasis and by face, buttocks or intergluteal and feet involvement (p<0.0001). Finally, physician and patient assessments were compared showing frequent mismatch and a scattered dot plot: PhysGA vs PGA (r=0.36), PhysMSK vs PMSK (r=0.39), PhysSk vs PSk (r=0.49).

Conclusion. PhysGA assessed by means of VAS is a reliable tool to assess musculoskeletal and dermatological disease activity. PhysGA may diverge from patient self-evaluation. Because musculoskeletal and skin/nail disease activity may diverge it is suggested that both PhysMSK and PhysSk are assessed.

Key Indexing terms:
Psoriatic Arthritis, Assessment Measures, Domains, Instruments, PhysGA

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Running footline:

Physician global assessment in PsA

Psoriatic Arthritis (PsA) is a frequent and potentially disabling chronic inflammatory disease affecting the musculoskeletal system (peripheral joints, digits, spine, entheses), skin, and nails (1,2).

In the last decade, disease assessment research has yielded improved stratification of PsA manifestations into discreet clinical domains, in order to more comprehensively assess disease activity with reliable outcome measures for randomized controlled trials (RCT) and longitudinal observational studies (LOS) as well as routine management (3). They include peripheral arthritis, enthesitis, dactylitis, axial disease, skin and nails, as well as a variety of patient reported domains such as fatigue, function, and quality of life, Efficacy of approved and emerging medications for the treatment of PsA clinical domains, utilizing these outcome measures, has recently been demonstrated in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations (4).

GRAPPA is comprised of members from different professional backgrounds, including rheumatologists, dermatologists and other investigators (5) and among its aims includes the validation and standardization of outcome assessment tools in PsA and Ps. In 2007 GRAPPA and OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials), after a multistep process (6-8), reached consensus on a core set of 6 domains to be measured in all clinical trials. These included peripheral joint activity, skin activity, pain, patient global assessment (PGA), physical function and health-related quality of life. Several other domains such as spinal disease, dactylitis, enthesitis, fatigue, nail disease, radiography, acute phase reactants and physician global

assessment, were considered important, not mandatory, but preferably assessed at some point in a clinical trial development program. More recently OMERACT members voted that the PsA core set should be revised because of the updated knowledge about PsA but in particular because of the strong feeling that the patient input needed to be incorporated more strongly (9). The new final core set included 3 parts: an inner group of domains to be measured in all RCT and LOS, including musculoskeletal disease activity (peripheral arthritis, dactylitis, enthesitis and axial symptoms), skin disease activity (skin psoriasis and nail dystrophy), pain, PGA, physical function, health-related quality of life, fatigue and systemic inflammation; a middle circle of domains, important but not mandatory, including economic costs, emotional well-being, participation and structural damage; an outer circle represents the research agenda (stiffness, independence, treatment burden and sleep) (10) (Table1).

The Physician Global Assessment (PhysGA) has been removed from the revised Core Domain Set and a preponderance of objective and patient reported outcomes measurements (PROs) is now evident. PhysGA of disease summarizes physician clinical assessment and incorporates patient feedback to the doctor and is therefore a major determinant which can influence therapy choice and general management. The deletion of PhysGA as a domain item is therefore of note, given that physician judgment in the recommendation of and taking responsibility for treatment is important Notably, previous studies have shown a discordance between patients and physicians assessment in arthritis, raising important questions of the consequences in treatment decisions (11).

Following GRAPPA input we have previously conducted a study which demonstrated that PGA by means of 0-100 mm visual analogue scale (VAS), taking into account both musculoskeletal and skin disease, was a reliable instrument to assess the burden of PsA disease (12). Given the relative independence of skin and musculoskeletal manifestations, it was proposed that in PsA, it is appropriate to assess the impact of dermatologic and musculoskeletal involvement segregated into 2 separate questions, one addressing MSK, and one addressing the skin. We further analyzed the data collected during the GRAPPA PGA study following the same methodology and focusing on the global evaluation of PsA disease activity from the physician point of view in order to validate the instrument, and finally to compare the physician perspective with the patient perspective by means of these two instruments.

PATIENTS AND METHODS

Patients. Patient selection and methodology was previously described in details (12). Briefly, 319 consecutive patients (58% male, 42% female; mean±SD age 51±13) fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR) (2) were enrolled in 16 centres from 8 countries worldwide (Italy, USA, Canada, The Netherlands, New Zealand, Germany, Brasil and United Kingdom). Seventeen centres were rheumatology units; only one centre was a dermatology unit, but the local investigator is also a Rheumatologist and performed the assessment of the enrolled patients. Consecutive PsA patients were included in the study regardless of disease activity, treatment and clinical subsets, as defined according to Moll and Wright (1) (for details, see table 2 reported in reference 12).

Questionnaires. Physician perception of disease was investigated following specific questions by means of 0-100 mm VAS as a global score (PhysGA), encompassing both joints (regarded as all musculoskeletal manifestations therefore including peripheral joints, dactylitis, enthesitis and axial, in order to keep it simple, as suggested by the patients), and all aspects of skin disease (including nails), as well as a question specific to joint manifestations and skin (PhysMSK and PhysSk, respectively) (Table 2). The questionnaires were elaborated by “expert opinion” consensus among GRAPPA members. In non-English speaking countries the coordinator of the centre was responsible for the process of translation/back translation of the questionnaires. The questionnaires, related to the degree of disease activity, were administered at baseline and after one week, without any change in treatment, in order to test the reliability of the instrument. The one week interval was selected as a good compromise

in order to avoid the repetition of the previous score by the physician and modification of disease activity. The three different VAS questionnaires were administered on the same day of the clinical examination, in a changing random order to exclude any bias.

Clinical assessment. Detailed clinical evaluation was performed according to a specific protocol. Demographic data and past medical history were taken at baseline. Joint disease clinical subsets were defined according to Moll and Wright (1). Musculoskeletal manifestations were objectively evaluated by means of the American College of Rheumatology (ACR) joint count (68 tender, 66 swollen) for peripheral joint, dactylitis and enthesitis were also clinically assessed (presence or absence) and detailed in the CRF, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was employed in patients with axial involvement as this instrument has been shown to be reliable in PsA (13). Skin psoriasis was evaluated by means of PASI (14). Involvement of face, genitalia, hands, buttocks/intergluteal or foot involvement was also recorded. Drug treatment at time of enrolment was detailed.

Statistical analysis. Descriptive analysis was performed expressing variables as mean ± standard deviation, or median with 25° and 75° percentiles, according to data distribution. Intraclass correlation coefficient (ICC) was used to assess the concordance between VAS score at week 0 and at week 1. Pearson correlation analysis was carried out in order to evaluate the strength of association between PhysMSK and PhysSk as well as PhysGA vs PGA, PhysMSK vs patient (P)MSK and PhysSk vs patient (P)Sk.

The influence of PhysMSK and PhysSk on PhysGA was analysed through a multiple linear regression. PhysMSK and PhysSk were considered as independent variables, while PhysGA was the dependent variable. A multiple linear regression was

also carried out to estimate the influence of gender, age, job (manual, intellectual, contact with public), dactylitis (presence vs absence), enthesitis (presence vs absence), number of tender joints, number of swollen joints, arthritis duration, PASI score, ~~and~~ areas of body surface involved (face, genitalia, hands, buttocks and/or intergluteal, feet) and psoriasis duration on PhysMSK and/or PhysSk.

Kruskall-Wallis test was performed to analyse differences in values of a continuous variable (PhysMSK, PhysSk) between clinical subsets.

Ethics:

Ethical Committee Approval was obtained in the following Centres: Johns Hopkins University, Office of Human Subjects Research, Institutional Review Boards, Study #: NA_00026662; Toronto University Health Network Research Ethics Board #08-0630-AE; Medical Ethical Committee of the Academic Medical Centre/University of Amsterdam (ref: MEC 05/162, ISRCTN23328456); and New Zealand Central Region Ethics Committee (approval number CEN/06/03/016). In the other participating Centres Ethical Committee Approval was not required in accordance with the policy of the Institutions and local legislation for this kind of study.

RESULTS

Eighteen centres from ten countries participated to this study. A total of 319 PsA patients gave informed consent and were included in the analysis. Musculoskeletal involvement: median number of tender joints was 5 (1-13), median number of swollen joints was 1 (0-5), axial involvement was reported in 8%, dactylitis was present in 7% and enthesitis in 21% of patients. Skin involvement: median PASI score was 2.8 (0.7-6.5) in overall cohort and 4.0 (2.0-5.2) in the single dermatology unit (p= ns). Face, hands, buttocks/intergluteal, genitalia and feet involvement was reported in 13%, 24%, 18%, 5% and 19% of the patients, respectively. Patients treatment was as follows: 63% of the patients were on csDMARDs, 23% on bioDMARDs, 37% on NSAIDs and 9% were on steroids. Detailed clinical data of the patients have been described previously (12). Median baseline values for the three questionnaires were as follow: PhysGA 32 (19-50), PhysMSK 25 (11-47), PhysSk 20 (9-40).

Test/retest. The ICC coefficients revealed good reproducibility of the VAS measures. ICC for PhysGA was equal to 0.90 (C.I. 95% 0.86-0.92); ICC for PhysMSK was equal to 0.86 (C.I. 95% 0.81-0.89); ICC for PhysSk was equal to 0.67 (C.I. 95% 0.58-0.75).

Physician global assessment. In order to quantify the specific influence of the musculoskeletal and skin component in the PhysGA of disease, we performed a multiple linear regression analysis. The final regression model was statistically significant, $p< 0.0001$ and R^2 0.78. The analysis showed B coefficient 0.69 (C.I. 95%

0.64-0.74) for PhysMSK and B coefficient 0.32 (C.I. 95% 0.27-0.37) for PhysSk, meaning that the musculoskeletal component is perceived as the dominant clinical issue compared to psoriasis.

Physician assessment of joint disease. In order to test the specific influence on PhysMSK of swollen and tender joints, dactylitis, enthesitis, arthritis duration, patient gender, age and job, a multiple linear regression was performed. Enthesitis, arthritis duration, gender, age and job were not significantly associated with PhysMSK, and therefore were eliminated from the model. The final regression model ($p< 0.0001$) included swollen joints, tender joints and dactylitis. The R^2 value was 0.34; the regression coefficients were B 1.66 (C.I. 95% 1.19-2.12) for swollen joints, B 0.27 (C.I. 95% 0.05-0.49) for tender joints; and B 9.60 for dactylitis (C.I. 95% 2.64 -16.56).

Furthermore, patients were also grouped according to number of joints involved: 1-3 joints (median PhysMSK 10 and 15.5, tender and swollen respectively); 4-5 joints (median PhysMSK 20.5 and 35.5, tender and swollen respectively); more than 5 joints (median PhysMSK 39 and 52.5, tender and swollen respectively), showing higher VAS scores for patients with more joints involved ($p<0.0001$). Involvement of metacarpal phalangeal joints, wrist and proximal interphalangeal joints of hands and feet, were perceived as associated with more severe disease.

The detailed median PhysMSK in the different clinical subsets were as follow: Polyarticular 27 (15-46), Oligoarticular 20 (7-40), Axial 40 (21-55), Distal 30 (20-50), Mutilans 44 (8-71), more than one subset 25 (11-41), with no statistically significant differences.

Physician assessment of skin disease. In order to test the specific influence on skin physician assessment of PASI score, involvement of face, genitalia, hands, buttocks and/or intergluteal and feet, psoriasis duration, patient gender, age and job, a multiple linear regression was performed. Hands and genitalia skin involvement, psoriasis duration, gender, age and job, were not significantly associated with PhysSk, and therefore were eliminated from the model. The final regression model ($p< 0.0001$) included the four independent variables PASI score, face, buttocks or intergluteal and foot involvement (R^2 value 0.61). The regression coefficients were B 2.47 (C.I. 95% 2.19-2.76) for PASI, B 6.62 (C.I. 95% 1.34 - 11.91) for face involvement, B 6.93 (C.I. 95% 2.32 - 11.55) for buttocks or intergluteal involvement and B 7.92 (C.I. 95% 3.18 - 12.67) for foot involvement.

The detailed median PhysSk in the different clinical subsets were as follow: Polyarticular 17 (9-40), Oligoarticular 12 (4-31), Axial 30 (13-55), Distal 20 (10-53), Mutilans 36 (8–55), more than one subset 25 (11-40), with no statistically significant differences.

Musculoskeletal versus skin psoriasis. In order to investigate physician clinical perception of musculoskeletal disease compared to skin disease we correlated PhysMSK and PhysSk assessment. The analysis revealed that, according to clinical judgement, musculoskeletal and skin disease do not correlate in terms of disease activity as evidenced by the correlation coefficient value between PhysMSK and PhysSk which resulted $r=0.24$ **,** with a marked scattered pattern at the dot plot (Figure N. 1).

Physician assessment compared with Patient self-assessment. In order to test the possible agreement or disagreement in global, musculoskeletal or skin evaluation by physician compared to patient self-assessment, we correlated PhysGA vs PGA (r=0.36), PhysMSK vs PMSK (r=0.39) and PhysSk vs PSk (r=0.49), by means of Pearson's test (the ideal concordance would be r=1). A marked scattered pattern of the dot blots (mainly in the lower/right part of the graph indicating higher values scored by the patients) is clearly visible, indicating a poor correlation between physicians and patients evaluation (Figure N.2a, b, c).

DISCUSSION

The assessment of PsA poses a challenge to the clinician because of its varied manifestations including peripheral joints, axial disease, enthesitis, dactylitis and dermatological manifestations.

In the recent past, it has been clearly observed a trend to include more PRO in general and even domain specific assessment of diseases, such as joint count in rheumatoid arthritis (15), although the data available in the literature is controversial (11, 16). More recently Salman R et colleagues (17) have conducted an elegant study comparing the degree of agreement between patient and physician in evaluating joint disease activity and damage as well as the degree of skin disease. They concluded that PsA patient self-report evaluation has a poor correlation with physician assessment and therefore expert physical examination should remain the gold standard for the assessment of actively inflamed join and skin disease. Several other studies have been performed in order to define if patient evaluation, given the emotional component and the difficulties to differentiate between possible multiple sources of symptoms, is accurate and in line with physician evaluation. Furst et al. found that among 305 paired patient-physician records analysed 23% were misaligned mainly because of a higher perception of disease activity and disability by the patients (18), while Eder et al. reported that fatigue, pain, disability and joint counts were the most important factors responsible to discrepancy between patient and physician joint assessment (19). On the other hand, Dandorfer et al found good correlations of patients and physician assessment of disease when using VAS scores, although physician usually evaluated

the disease activity of PsA lower than the patients (20), as reported also by Destieux et al. (21).

Physician perception of disease activity, following history taking and objective examination of the patient including laboratory and imaging evaluation, is partly independent of patient self-assessment, and thus should be factored in the determination of clinical management and treatment proposition to the patient. PhyGA and PGA are both reliable instruments for assessing disease activity, but they do not overlap reflecting the two slightly different sides of the same coin.

The 100 mm VAS is recommended, over a 5-point Likert and 11-point numeric rating scale, as the instrument for the PGA and PhysGA domain because of demonstrated psychometric quality in RA and OA (22-23). Reliability was determined by test-retest.

Our present study demonstrated that PhysGA assessed by means of VAS is a reliable tool related to both MSK and dermatological disease activity. Because MSK and skin disease very often diverge it is suggested that both PhysMSK and PhysSk are also evaluated separately for a more detailed analysis of the physician perspective.

The specific influence of the joint and skin components in the physician global perception of disease was evaluated by multiple linear regression analysis. It should be emphasized that PhysMSK and PhysSk explain nearly all the variance in PhysGA (r-squared of 0.78). It also showed a preponderance of the arthritis symptoms over the skin, which is not surprising given the low PASI scores found in the majority of the patients attending rheumatology clinics, and broadly speaking in the PsA population in general. It is noteworthy that 17 out of 18 centres of the consortium were Rheumatology

Units rather than Dermatology Units, and therefore this could represent a bias in the recruitment process which may explain a more severe joint disease. On the other hand, many patients recruited by the rheumatologists were also followed by a dermatologist, and it is unlikely that patients with arthritis are followed only by a dermatologist. For these reasons we believe that our cohort of patients well represents the general population of PsA patients.

Further analysis of the assessment of joint disease by the physician showed that statistically significantly higher values of VAS scores correlated with the number of joints involved, supporting the validity of the instrument (VAS) for the domain of interest (physician joint assessment). Furthermore, there was no relationship to a particular subset of clinical type of PsA. Indeed, patients belonging to the mutilans subset had higher scores followed by patients of the axial subset, but without statistical significance.

It is noteworthy that the occurrence of dactylitis, in our cohort, was perceived by the physician as severe. Dactylitis is a typical clinical feature of PsA (being present in 16-48% of cases) and can be considered a clinical indicator of disease severity (24). On the other hand, the presence of enthesitis, arthritis duration, gender, age and job of the patient did not influence physician perception of joint disease.

A similar approach was followed to analyse physician assessment of the impact of skin disease in relation to the degree of skin psoriasis by means of PASI, involvement of face, genitalia, hands, buttocks and/or intergluteal and feet, psoriasis duration, gender, age and job. A significant association was found for PASI score and involvement of the face, buttocks or intergluteal, and feet, showing R^2 value 0.57, indicating that these variables accounted for 57% of the total variation in PhysSk. PASI

scores do not differentiate on the basis of the involved area, but the physician perception of disease severity clearly is also dependent on the involvement of precise areas, not simply on the “amount” of involved skin. In this study the site of major impact on physician perception were the face, buttocks, intergluteal and feet, probably because of their role in working, life activities, hygiene and also in social interaction. It should be underlined that these findings derived from a cohort characterised by a low PASI score, as typical in PsA patients.

We further investigated the impact of arthritis compared to skin psoriasis. The analysis revealed that joint and skin disease did not correlate in terms of disease activity, a finding consistent with other studies (25). Some synthetic DMARDs work better for one manifestation but not the other, such as cyclosporine-A for the skin and leflunomide for the joints (26, 27) and the same is true for some biologics (4). Genetic factors may also differ, as well as immune cells implicated in disease pathogenesis (28, 29). Several clinical and experimental evidences suggest that different mechanisms drive the joint and skin processes, but the lack of knowledge of the causative agent(s) does not allow testing of this hypothesis. The lack of correlation between the joint and skin disease scores (objective but also perceived by the treating physician) raises the point that although the PhysGA performed well overall in our study as a single measure, a more complete assessment may be derived from also measuring PhysMSK and PhysSk, for example in the circumstance that drug may improve one of these domains but not adequately the other.

Finally, this study has underlined the frequent discordance between physician and patients in the evaluation of PsA. Patients are prone to score a higher burden of

disease compared to physician evaluation. The reasons that may explain this discrepancy are several, physicians may have seen worse cases or may be used to treat other more life-threatening disease, while patients do consider their everyday disease and difficulties as reference. This mismatch has critical consequences given the fact that is the physician who proposes the treatment approach to the patient, and takes the responsibility for the prescription.

In conclusion PhysGA, as well as PhysMSK and PhysSk separately, are reliable in PsA. Although the PhysGA as a single measure was demonstrated to perform well in assessing the patient in totality, it was also demonstrated that physician assessment of joint and skin disease activity may be divergent. Therefore, although PhysGA is an acceptable single measure for clinical trials and clinical practice, in situations such as the study or common use of a drug which may improve the joints but not the skin, it would be important to assess both the PhysMSK and PhysSk as well.

FOUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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