PSORIATIC ARTHRITIS (PSA) AND OUTCOME MEASURES

Cauli A, Porru G, Piga M, Vacca A, Mathieu A.

Alberto Cauli MD PhD (cauli@medicina.unica.it)
Giovanni Porru MD (giovaporru@yahoo.it)
Matteo Piga MD (matteopiga@alice.it)
Alessandra Vacca MD (ales.vacca@tiscali.it)
Alessandro Mathieu MD, Professor of Rheumatology (mathieu@medicina.unica.it)

Rheumatology Unit, Department of Medical Sciences, Policlinico of the University of Cagliari, ss554 Monserrato 09042 Italy.

Running title: Assessment in Psoriatic Arthritis

Key Indexing words: Psoriatic Arthritis, Outcome Measurements, Domains, Instruments.

Address to correspondence and request for reprints:
Alberto Cauli MD, PhD,
Department of Medical Sciences
Rheumatology Unit, Policlinico of the University of Cagliari,
ss 554, Monserrato 09042 - Cagliari, ITALY
e-mail: cauli@medicina.unica.it
Phone and fax: +39 070 5109 6383 - mobile: +39 348 410 9449

ABSTRACT

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by arthritis associated with skin psoriasis and several extra-articular manifestations. The clinical complexity of this disease is mirrored in the difficulties of its assessment, which ranges from peripheral and axial arthritis to enthesitis, dactylitis, skin and nails lesions, and patient perception of disease (i.e. fatigue, pain, quality of life, functional and global status). This paper summarizes the main assessment tools available for PsA in clinical practice and research trials.
Psoriatic Arthritis (PsA) is a systemic inflammatory disease characterized by the prominent involvement of the peripheral and axial joint and by skin dermatitis (psoriasis, Ps). It is usually seronegative for rheumatoid factor and also for this reason has been included in the spectrum of the spondyloarthropathies which share this condition (SpA). According to the classical Moll and Wright classification (1), PsA may present different clinical pictures: peripheral joint arthritis (oligoarticular, polyarticular, distal or mutilans pattern) or inflammatory spinal disease. Overlap of clinical subtypes is common. Other clinical manifestations that deeply influence the clinical picture are: enthesitis, dactylitis, tendonitis, uveitis, features that are common to the other spondyloarthopathies such as ankylosing spondilitis (AS), reactive arthritis (ReA) and SpA associated with inflammatory bowel disease (IBD) (2).

The early immunological events in PsA pathogenesis are considered to take place largely on the basis of a genetic susceptibility (3,) and to be mediated by T cells (4) interacting with other cells (5), giving rise to the inflammatory cascade which then activate a wide range of pathways, leading ultimately to joint damage and repair mechanisms. Recently, increasing evidence has underlined the role of a new subset of T lymphocyte, named Th17 according to its signature cytokine, to the pathogenesis of PsA. It is noteworthy that when PsA patients present spinal involvement they often are positive for the HLA-B27 marker (6).

Clinical monitoring and assessment of response to drug treatment were influenced in the past by the lack of specific outcome measures for treatment. The need to test the efficacy and safety of new biologic agents in randomized controlled trials was the main force to trigger a collaborative effort to define domains and develop instruments which could effectively assess response to treatment. Furthermore new classification criteria were developed by the international multicentre (30 rheumatologists) CASPAR group (Classification of Psoriatic Arthritis) to differentiate PsA from other forms of arthritis (7).

In the last decade several Rheumatologist, Dermatologists and non clinical members joined in GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) with the aim to validate and standardize outcome assessment tools in PsA and Ps, both for clinical practice and for therapeutic investigative studies. Key domains for assessment of disease activity and response to treatment in PsA and Ps were identified through a multi step process by means of literature review (8) and a Delphi exercise (9). Further work took place during the first GRAPPA meetings and OMERACT modules in Asilomar (CA) (10) and Malta (11-12). Six domains were included in the inner circle of the core set of recommended domains to be assessed in randomized controlled trials and/or longitudinal observational studies in PsA. Eight domains were also considered important but not mandatory and were included in the outer circle. Five domains did not receive sufficient support for inclusion in the core set but were considered important and were placed in the research agenda (Table 1). Following this first stage GRAPPA set up committees to study old e new instruments to measure these domains. In this paper we review the assessment of the principal domains and the instruments useful in daily clinical practice and in research studies.

Assessment of peripheral joint
Several instruments have been applied in drug trials to point out treatment efficacy compared to placebo. Among these instruments the most popular are: the American College of Rheumatology (ACR) response criteria developed in patients with rheumatoid arthritis (RA) (13) and the Psoriatic Arthritis Response Criteria (PsARC) developed in patients with PsA for a trial testing sulfasalazine efficacy in PsA (14). These criteria include clinical assessment of swollen
joint count (SJC), tender joint count (TJC), patient and physician self assessments of global disease activity.

To satisfy the ACR20 (or 50 or 70) response criteria the patient must shows improvement ≥20% (or ≥50% or ≥70%) in both the swollen and tender joint counts, as well as a 20% (or ≥50% or ≥70%) improvement in 3 of the following 5 items: patient and physician global assessments of disease activity (by means of visual analogue scale, VAS), patient pain evaluated by means of VAS (0-100), Health Assessment Questionnaire (HAQ), and either erythrocytes sedimentation rate (ESR) or C-reactive protein (CRP). The PsARC measures swollen joint scores (SJS), tender joint scores (TJS), patient global assessment (on a 0-5 point scale) and physician global assessment of disease activity (on a 0-5 point Likert scale). A response is detected by a reduction of ≥30% in SJS and or TJS and reduction of at least 1 unit in Likert assessment scores. The overall response is fulfilled when improvement is present in 2 of the 4 items (one must be SJS or TJS) without worsening in any domain. Another instrument that has been proposed and applied in peripheral subset PsA is the DAS composite score which includes 44 SJC and TJC, or the simplified DAS28, a 28 tender and swollen joint count plus patient global assessment of well being and ESR or CRP (15). The DAS defines arthritis disease activity at time of visit, EULAR DAS response criteria consider the change from two distinct time points. Application of the DAS28 to PsA is not encouraged because of the limited number of joints evaluated. In clinical evaluation of PsA patients it is suggested to use the 68 joint count because it includes the majority of joints affected in PsA.

Recently, Philip Helliwell from Leeds University promoted a collaborative multi centre study (GRACE) addressing the issue of development of a new comprehensive disease severity and responder composite index for Psoriatic Arthritis (PsA) (16); work is still in progress.

Assessment of skin
Skin psoriasis is a major manifestation of disease in PsA, it is responsible of discomfort and may cause low quality of life. It is therefore important to evaluate skin involvement precisely and objectively. There are basically two approaches, one is subjective: patient and/or physician global assessment of disease activity and the other objective, photographs and or calculation of involved and severity of body surface area. Specific tools include Psoriasis Area Severity Index (PASI) (17), Lattice System Physician Global Assessment (LS-PGA) (18), and National Psoriasis Foundation Psoriasis Score (NPF-PS) (19). Despite the known deficiencies of PASI score, mainly low performances in patients with low degree and extent of skin psoriasis, PASI has functioned well in randomized clinical trial testing the efficacy of new biologic drugs in both in psoriasis and in PsA. Although it has limitations, PASI still remains the “gold standard”.

Patient Global Assessment of Disease Activity
Patient global assessment (PGA) has been included in inner circle of the core set of domains for the assessment of PsA by GRAPPA and OMERACT (12). Patient global assessment is useful and important because helps physicians to evaluate patient discomfort and to calibrate a more patient centered clinical and therapeutic approach. PGA has also been included in widely used composite indices developed for rheumatoid arthritis but also employed in PsA. Among these measures are the American College of Rheumatology (ACR) response criteria (13), the Disease Activity Score (DAS) (15) and the Psoriatic Arthritis Response Criteria (PsARC) (14). A collaborative study performed on patients enrolled in 18 centres from 10 countries worldwide assessed the reliability of the PGA, measured by means of 0-100 mm visual analogue scale (VAS), and the possible additional utility of separate VAS scales for joints and skin (20). The 100 mm VAS instrument was selected by GRAPPA for this domain, over a 5-point Likert and 11-
Assessment in Psoriatic Arthritis

Point numeric rating scales, because of its performance in RA and OA (21, 22). Reliability was determined by test-retest. It should be underlined that patient perception of joint disease and patient perception of skin disease explained nearly all the variance in PGA (r-squared of 0.73). The study also showed a major impact of the arthritis symptoms over the skin, which was expected given the low PASI scores found in the majority of the patients attending rheumatology clinics, and broadly speaking in the PsA population in general. The possibility that anxiety and depression could substantially affect the perception of the disease by the patients was evaluated and the results suggest that the PsA patients perception was unrelated with the mood status. Therefore the study demonstrated that PGA assessed by means of VAS is a reliable tool related to both joint and skin disease activity. Nevertheless, since joint and skin disease often diverge, it was suggested that both joint and skin should also be assessed separately for a more comprehensive analysis of the patient perspective, in particular in drug studies which may affect preferentially one compartment (20).

Assessment of Physical Function

Instruments for measuring physical function have been used and validated in PsA patients. They include the HAQ disability index and the SF-36 physical function (PF) subscale (23,24). The scores of both these instruments improve significantly following anti-TNF-alpha treatment, although the SF-36 PF scale appears to show better sensitivity to change (24).

Assessment of Health Related Quality of Life,

Several instrument explore health related quality of life (HRQoL). Among these the most applied tool is Medical Outcome Survey Short Form 36 (SF-36) which has been used in PsA (23). Other instrument of HRQoL have been employed in PsA drug trials, including the Dermatology Life Quality Index (DLQI) (25). The PsAQoL is the first disease-specific instrument which has been validated in PsA, and should now be applied to clinical practice and drug trial (26).

Assessment of Dactylitis

Dactylitis is a frequent and characteristic manifestation in PsA occurring in approximately one third of patients and is generally detected in active and severe disease (27). Dactylitis is generally assessed by its presence or absence, and some authors also propose a tenderness score. P Helliwell has proposed the Leeds Dactylitis Instrument (LDI) (28), developed to provide to clinicians a less subjective measure of the inflamed finger. It uses a special device to measure the diameter of digits on both sides and identifies a 10% difference in diameter as cut off to detect a swollen digit. The instrument includes a tenderness score. The LDI has been shown to have good inter- and intra-observer reliability.

Assessment of Enthesitis

Enthesitis is a common clinical manifestation in PsA and in SpA in general. Among instruments developed to quantifying enthesitis one of the first has been the Newcastle Enthesitis Index (NEI) developed by Mander (29) which consider 66 sites for enthesal assessment. Because it is time consuming a different index has been developed considering only 13 sites, the Maastricht AS enthesitis score (MASES) (30).

Both scores have been shown to be valid in an international study (The International Spondyloarthritis Interobersver Reliability Exercise, INSPIRE) to examine inter-rater reliability conducted in Toronto (31).

Enthesitis may be a very tricky clinical manifestation because its symptoms and signs may be hard to distinguish from those of fibromyalgia (FM). Patients with primary FM and associated
psoriasis, or with FM associated with PsA, or with psoriatic polyenthesitis may have similar clinical features and, therefore, they are at risk of misdiagnosis and bad management. For these reasons an Italian multicentre study led by Antonio Marchesoni aimed to identify which clinical features in patients with psoriatic arthritis (PsA) can help to make a diagnosis of associated fibromyalgia (FM). The univariate analysis showed that FM patients had higher mean values of tender points, enthesitic score, FM-related symptoms and a lesser response to NSAIDs. Presence of ≥6 FM-associated symptoms, ≥8 or more tender points, and no response to NSAIDs had the highest predictive value for FM at the multivariate analysis (32).

**Assessment of Axial involvement**

Psoriatic spondylitis is not as severe compared to spinal involvement in AS, presenting with less pain and lower functional limitation. Nevertheless some features of psoriatic spondylitis, such as asymmetrical sacroiliitis, non-marginal syndesmophytes, asymmetrical syndesmophytes, paravertebral ossification, and more frequent involvement of cervical spine are characteristic of PsA compared to AS and may help in the differential diagnosis in cases “sine psoriasis”. The prevalence of sacroiliitis mirrors the frequency of the HLA-B27 allele among patients.

For the clinical assessment of axial disease in PsA instruments borrowed from AS are generally applied: the occiput-to wall distance, chest expansion, modified Schober, and lateral spinal flexion (31). Moreover, the Andrew Calin composite index Bath Ankylosing Spondylitis Metrology Index (BASMI) including five measurements can also be applied.

Radiological assessment of the spine is not in the aims of this review, nevertheless it is noteworthy the recent collaborative work which recently has led Ennio Lubrano et colleagues to validate in PsA radiological indexes developed for AS, such as the Bath Ankylosing Spondylitis Radiology Index (BASRI) and the modified Stoke Ankylosing Spondylitis Spine Score (m-SASSS) (33), and to propose a new radiological index specific for axial PsA (34).

**Assessment of Nails**

Nail involvement in patients with psoriasis and PsA is frequent although it is rarely a problem which affect patient daily life. The most common assessment tool for nail psoriasis is the modified Nail Psoriasis Severity Index (m-NAPSI) (35). The m-NAPSI is a simple, numeric, reproducible and objective instrument specific for psoriasis. This scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit. M-NAPSI may therefore be implemented in clinical trials for evaluating response to treatment.

Recently nail involvement was evaluated in a cohort of 40 patients from the outpatient clinic of the University of Cagliari. Nail involvement was assessed as “modified nail psoriasis severity index” (m-NAPSI) and as “physician nail assessment” by mean of a 0-100 mm VAS. A strong correlation between the two instruments was observed, furthermore we observed a significant correlation between nail involvement and skin disease (evaluated by PASI) (36).

**Assessment of Fatigue**

Fatigue is an important clinical manifestation of almost all the inflammatory diseases, including PsA and chronic arthritides. Several instruments have been developed to assess this domain in different diseases such as Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-fatigue) (37), Multidimensional Assessment of Fatigue (MAF) scale, and Multidimensional Fatigue Inventory (MFI) (38). The FACIT-fatigue is the instrument mostly used in PsA, it has been employed in trials of adalimumab efficacy in PsA showing improvement of
fatigue following active treatment compared to placebo (39), furthermore the FACIT-fatigue scale is reproducible and correlate with other instruments for fatigue.

PsA is a systemic multidomain inflammatory disease characterized by involvement of joints (peripheral and axial), skin and nails, enthesis, and digits. GRAPPA, OMERACT and single researchers are working to further develop and validate outcome measures that may help clinicians in daily practice and in randomised controlled drug trials aiming to demonstrate the effectiveness and safety of new therapies on patients’ function and quality of life.
Table 1: Core Set of Domains for Psoriatic Arthritis

<table>
<thead>
<tr>
<th>INNER CIRCLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral joint activity</td>
</tr>
<tr>
<td>Skin activity</td>
</tr>
<tr>
<td>Patient Global (PGA)</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Physical Function</td>
</tr>
<tr>
<td>Health Related Quality of Life</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OUTER CIRCLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enthesitis</td>
</tr>
<tr>
<td>Dactylitis</td>
</tr>
<tr>
<td>Spinal</td>
</tr>
<tr>
<td>Nails</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Physician Global</td>
</tr>
<tr>
<td>Radiology</td>
</tr>
</tbody>
</table>

Other domains: magnetic resonance imaging, ultrasound, computed tomography, tissue analysis, participation.
REFERENCES


15) van Gestel AM, Prevo MLL van’t Hof MA, van Rijswijk MH, van de Putte LBA, van Riel PLCM. Development and validation of the European League Against Rheumatism response

Revista Latinoamericana de Psoriasis y Artritis Psoriásica 2012, 5: 1-10
http://www.fmv-uba.org.ar/


