Assessment of disease activity in psoriatic arthritis

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Received and accepted on August 20, 2015.
Clin Exp Rheumatol 2015; 33 (Suppl. 93): S44-S47.
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Key words: psoriasis, psoriatic arthritis, disease activity

ABSTRACT
Psoriatic arthritis (PsA) historically has been assessed according to disease activity measures borrowed from rheumatoid arthritis. However, more disease activity measures specific to PsA have been developed. This development is appropriate, as the disease is not confined to the joints but has multiple manifestations, in addition to skin and joints. Assessments of disease activity are unique to each domain. Including different domains in composite measures increases the level of complexity. This review briefly discusses the available outcome measures, both within domains and as composite measures, and discusses likely future directions.

Introduction
Psoriatic arthritis includes a wide variety of clinical manifestations, each of which may vary, at any one time, in activity and impact both within and between individual patients. For example, in one person the skin may be the most severely affected, in another the joints, and these manifestations may also vary with time in an individual patient. Thus, assessing disease activity must account for different manifestations, since all may contribute to the overall disease impact.

Highly effective treatments are now available for psoriatic arthritis, and research in this field is expanding. Patients are now anticipating that drugs will be effective for all the disease manifestations, including skin and joints, and hope they may also be beneficial for co-morbidities and extra-skeletal manifestations. Therefore, it is important in both phase II and phase III studies to ensure all aspects of disease activity are assessed.

The work of the Group for Research and Assessment of Psoriasis and Psoriatic arthritis (GRAPPA) has been pivotal in this regard, starting with the identification of the core domains to be included in clinical trials (1). It is fitting that these core domains are now due to be updated and revised at the 2016 Outcomes in Rheumatology Clinical Trials (OMERACT) meeting.

Rheumatoid arthritis measures
Measurement of disease activity in rheumatoid arthritis is most often represented by the disease activity score for 28 joints (DAS28) (2). Initially thought to be impossible to use outside the clinical trial environment the DAS28 has gained widespread use in some routine clinic settings. The need for a concurrent acute phase response has limited its ‘real time’ use, but familiarity, ease of calculation (with hand held or on-line devices), availability of response criteria and cut-offs all have strengthened the use of the measure. In fact, such has been the popularity that the DAS28 has been introduced as a disease activity measure in PsA, both in clinical trials, in registries, and in routine clinics. Although Fransen et al. have demonstrated that the DAS28 is informative as a disease activity measure in PsA it should be noted that the data on which this conclusion was based were taken from clinical trials in which most of the patients had polyarticular disease (3). The DAS28 may not function as well in oligoarticular disease, which can be seen in up to a third of patients presenting with PsA. Indeed it has been shown that in this scenario up to 20% of patients may be misclassified in terms of disease activity (4). Alternative, rheumatoid specific, disease activity measures, such as the CDAI have also been used in registries, such as CORRONA, but are not validated for use in PsA although the same caveats apply: they do not measure across the disease spectrum.

Joint counts
Although a 28, or even 44, tender and swollen joint count may function
equally well in rheumatoid arthritis, because of the relatively oligoarticular presentation of PsA a full 66 tendon and 68 swollen joint count is recommended (5). In addition, an assessment of axial disease should be made, if appropriate, as up to 40% of patients with PsA may have axial involvement. In this context it is worth noting three other observations. Firstly, patients with PsA may have less tenderness of their joints than people with RA and a uniform approach to eliciting joint tenderness must be made (pressure sufficient to blanch the examiners nail is roughly equivalent to a force of 40N, or 4kg) (6). Secondly, a digit with dactylitis may have a number of concurrent pathologies, and may have one, two or all three joints involved with synovitis. Thirdly, it is important to distinguish joint tenderness from peri-articular enthesal tenderness – at the shoulder, knee and elbow this may be particularly relevant as some of the enthesal insertions (e.g. at the greater tuberosity of the humerus) are intimately associated with the joint.

Skin
The psoriasis area and severity score (PASI) has traditionally been used to measure disease activity of the skin in clinical trials (7). The limitations of the PASI have been well described. Particular problems are the non-linear scale, poor responsiveness in mild disease and lack of weighting for areas such as the face, hands and genitals. From a rheumatologic point of view it is worth noting that most of our patients with PsA have relatively mild skin severity, and it is at these low levels of skin disease activity that the PASI is less reliable and less responsive. Dermatologists rarely use the PASI in the routine clinical care. A number of other disease activity measures have been suggested for the clinic use but the adoption of the PASI as a threshold measure for biologic agents in certain countries (https://www.nice.org.uk/guidance/ta146/chapter/1-Guidance) has meant that this measure continues to be used. Simpler alternatives include the body surface area, although this does not take into account the disease activity of individual plaques but merely measures the extent of involvement. Both patient and physician global visual analogue scores are used, as is a physician ‘clear or almost clear’, although there are clear limitations of the latter in measuring across the spectrum of the disease.

Enthesitis
Enthesitis is problematic. Although considered by some to be the primary lesion in PsA and other spondyloarthropathies clinical assessment for active disease is not straightforward. There are literally hundreds of entheses palpable around bony prominences of the skeleton and, in theory, any of these may be affected by inflammatory change. There are two main problems with assessing active enthesitis: firstly, there is a poor concordance between tenderness at enthesal insertions, and objective evidence using imaging, mainly imaging with ultrasound. The most reliable data occur at the Achilles insertion where power Doppler signal is moderately related to tenderness (8). The second problem is the increasing prevalence of degenerative enthesopathy with age, particularly at the medial and lateral epicondyles of the elbow, and the plantar fascia (9). Despite these limitations, a number of clinical enthesitis indices are in use in clinical trials. Which of these performs best in practice? The data are inconclusive. In development, the Leeds Enthesitis index (six sites comprising both lateral epicondyles of the elbow, medial condyles of the femur and Achilles tendon insertions) compared well to the other indices available at the time, with an effect size of 0.82. The main alternatives are the Maastricht index (MASES(10)) and the Spondyloarthropathy Research Consortium of Canada (SPARCC(11)) index, both of which have more applicability to spondyloarthropathy in general, and more sites, the MASES 13 and the SPARCC, 18. The juxta-articular position of some entheses may result in difficulty in assessing tenderness in the presence of associated joint inflammation – this may in particular be true for the LEI, although more recent evidence does not support this (8).

Dactylitis
Dactylitis is a hallmark feature of PsA and serves as a paradigm of disease pathology. MRI studies of digits with dactylitis have shown a multitude of abnormalities, which reflect the underlying disease mechanisms. In an active inflamed dactylitic digit it is common to find osteitis, synovitis, enthesitis, tenosynovitis and soft-tissue inflammation (12). A simple count of digits involved by dactylitis is commonly made but this method relies on a reliable identification of dactylitis. Unfortunately, inter-rater assessment of dactylitis is poor (13). To overcome this problem an objective measure of dactylitis was introduced: the Leeds Dactylitis Index. This method not only provides a semi-quantitative assessment of dactylitis but also provides an objective appraisal of a digit, thus removing the poor inter-rater assessment (14).

Axial disease
No PsA specific measures of axial disease activity have been developed to date (5). Disease activity in this domain thus relies on measures developed for use in ankylosing spondylitis: and in particular the Bath ankylosing spondylitis disease activity measure (BASDAI (15)) and the Ankylosing spondylitis disease activity score (ASDAS (16)). Unfortunately, it seems as though the BASDAI is influenced by peripheral joint involvement in psoriatic arthritis and may therefore not be a valid assessment of axial disease activity (17).

Patient reported outcome measures
In a multinational study under the auspices of GRAPPA, Cauil et al. explored the contribution of three different visual analogue scores to the patient reported assessment of disease activity: a skin VAS, a joint VAS and a global VAS (18). Although there was a certain amount of redundancy in the use of all three scores together, the study demonstrated that it was important to assess disease activity in all three domains, as disease activity across the domains may diverge. In the subsequent GRAPPA composite exercise (GRACE) study the patient global VAS was the main predictor of treatment change in a mul-
tivariable model and was thus incorpo-
rated in the composite measure called 
the Psoriatic arthritis disease activity 
measure (PASDAS) – see below. 

Composite scores 

Composite scores are a more efficient 
way of assessing disease activity. By 
putting different assessments together 
into one index the sum performs better 
than the individual parts. With larger ef-
fect sizes, sample sizes become smaller. 
In a disease such as PsA, in which dis-
ease manifestations are heterogeneous, 
the challenge is not only conceptual 
but practical. What, for example, if one 
aspect of the disease (say the skin) 
responds differently to another (say the 
joints)? The net effect might be no 
change in the index. This scenario is ac-
tually less likely than one in which one 
domain changes and the other doesn’t, 
thus somewhat negating the purpose of 
a composite index. 

In the GRACE study two new compos-
te indices were derived from the data: 
the PASDAS and the GRACE index (19). A third, the Composite psoriatic disease activity index (CPDAI (20)) was also validated in this dataset. In a subsequent paper cut-offs for response and disease activity were developed (21). GRAPPA has also supported the development of a low disease target for use in clinical trials: the minimal dis-
ease activity criteria (MDA (22)). The properties of all these composite indi-
ces are similar – they measure across 
the disease spectrum and, apart from 
the MDA criteria, can act as disease 
activity, state and responder indices. 
Validation of the composite indices has 
been undertaken: it is clear that achiev-
ing a good treatment response by any of 
these measures is associated with less 
radiographic damage, in the clinical 
trial situation (23-25). 

Conclusions and future 
considerations 

The challenges of assessing disease 
activity in such an heterogeneous dis-
ease as PsA are legion but in the last 
10 years GRAPPA has helped develop 
new outcome measures across the dis-
ease spectrum. There remains the prob-
lem of utilising composite scores that 
function efficiently. In this scenario the 
skin component is most problematic 
in that skin involvement in most cases 
of PsA seen in rheumatology clinics is 
minimal, and the skin may not always 
respond synchronously with the muscu-
loskeletal manifestations. However, 
the paradox of early skin response to some 
therapies, such as methotrexate, can 
lead the observing physician into a false 
impression that all components of dis-
ease have improved. Only by systemat-
ically, and objectively, measuring these 
individual components can an accurate 
appraisal of disease activity be made. 
Putting all the assessments together in 
a composite index is, for now, probably 
only done in the context of clinical tri-
als, but trends may change. MDA as a 
suitable target for treatment outcome 
has been used in a strategy trial (26), 
and a trial of treatment withdrawal (27), 
and may be a feasible outcome in the 
routine clinic situation. 

For the future, the development of a 
new core set of domains, under the 
auspices of the OMERACT group will 
necessitate a re-appraisal of the current 
composite measures. The challenge will 
be to strike the correct balance between 
comprehensiveness and feasibility. 

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S-46