Optimisation of rheumatology indices: dactylitis and enthesitis in psoriatic arthritis

E.G. Ferguson, L.C. Coates

Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Chapeltown Road, Leeds, United Kingdom.

Esme G. Ferguson, BSc, MBChB, MRCP
Laura C. Coates, MBChB, PhD, MRCP

Please address correspondence to:
Laura C. Coates,
Leeds Institute of Rheumatic and Musculoskeletal Medicine,
University of Leeds,
Chapel Allerton Hospital,
Chapeltown Road,
Leeds LS7 4SA, United Kingdom.
E-mail: l.c.coates@leeds.ac.uk

Received on September 2, 2014; accepted in revised form on September 10, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 85): S113-S117.

Key words: psoriatic arthritis, enthesitis, dactylitis, outcome measures, clinical assessment

Competing interests: none declared.

ABSTRACT

Outcome measures are a key part of study design and clinical assessment. Enthesitis and dactylitis are typical features of psoriatic arthritis (PsA) and the spondyloarthritides but traditionally scoring systems for enthesitis have mainly been validated in ankylosing spondylitis (AS). There are many scoring systems which are not validated used for dactylitis although newer validated scores are now available. Recently there have been advances in composite scores that include enthesitis and dactylitis to assess disease activity. These are currently being validated further and have not yet been tested in routine clinical practice.

Introduction

Psoriatic arthritis (PsA) is an immune mediated disease in which there is heterogeneity in its presentation and course, which contributes to the complexity in diagnosis and assessment of PsA. The key clinical features of PsA include joint, skin, nail, axial disease, enthesitis, and dactylitis. Diagnosis of PsA based on the Classification of Psoriatic Arthritis (CASPAR) Study Group criteria has been well validated (Table I) (1, 2).

Outcome measures used in clinics and research trials are well established in RA and AS. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the Outcome Measures in Rheumatology clinical trials (OMERACT) have identified a core set of domains for PsA to be assessed in clinical trials, including dactylitis and enthesitis (Fig. 1) (3). Over the last decade clinical outcome assessments for PsA have evolved.

Enthesitis

Enthesitis is a recognised important manifestation of spondyloarthropathies characterised by inflammation at sites of attachment to bone of tendon, ligament, or joint capsule (4). This can cause pain, tenderness, and swelling at these sites and is estimated from registry data that 30–50% of patients with a diagnosis of PsA have enthesitis (5).

The use of clinical assessment tools for enthesitis has now become widespread in clinical trials despite the debate about which particular scoring system is optimal. In particular, establishing criterion validity has been difficult because of a lack of gold standard. Ideally a gold standard would have associated evidence of tissue abnormality from histopathology studies. However biopsy of tendons is neither safe nor easy, and there are limited research data available. MRI has been shown to identify bone marrow oedema at tendon insertions and abnormal signal around the enthesis (6). Ultrasound scanning using grey-scale and power Doppler to identify increased vascularisation in and around the enthesis can identify abnormal findings in symptomatic and asymptomatic entheses (7). Given that ultrasound identified power Doppler signal, and MRI bone marrow oedema have been correlated with tissue evidence of inflammation in other rheumatic manifestations, it seems likely that imaging is the best *gold standard* available at present (8). However correlation of imaging with clinically appreciable tenderness or swelling is limited particularly in enthesitis, which may have implications for validation of clinical measures (9). In addition to the soft tissue changes visualised, MRI scanning has identified the involvement of bone adjacent to the enthesis. No studies have addressed whether this can be clinically identified and whether it correlates with clinical enthesitis counts. Studies have also shown that ultrasound indices for enthesitis such as the Madrid Sonographic Enthesitis Index (MASEI) can differentiate between

Table I. CASPAR Criteria.

Domains	Description
Essential Criteria Inflammatory (≥1 needed)	
1. Inflammatory Joints	
2. Inflammatory axial disease	
3. Entheseal disease	
Additional Categories (≥3 points needed)	
1. Psoriasis	
• Current	Skin/scalp psoriasis present
	History of psoriasis
• History	History of psoriasis in first or second degree relative
• Family history	
2. Psoriatic nail involvement	Typical Psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis observed on current examination
3. A negative test for RF	
4. Dactylitis	Swelling of an entire finger
• Current	A history of dactylitis recorded by a rheumatologist
• History	Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of a hand or foot.
Radiological evidence of juxtaarticular new bone formation	

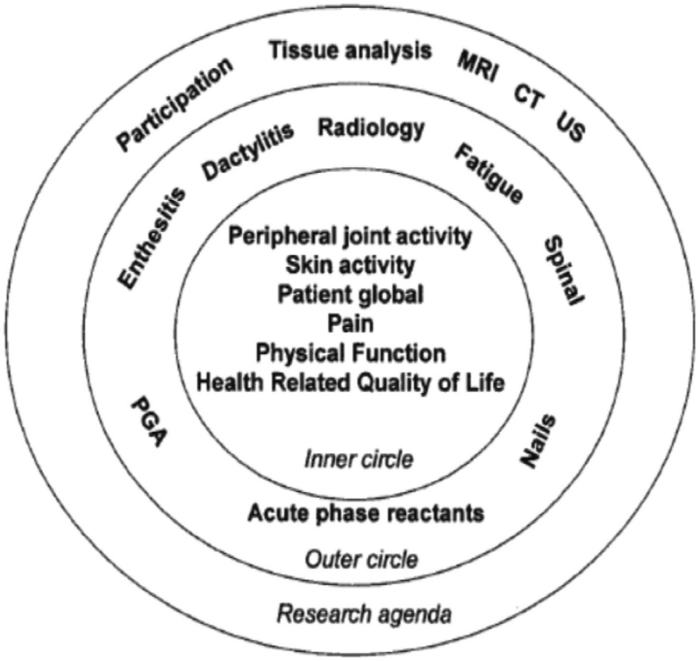

Fig. 1. Domains for Psoriatic Arthritis (3).

those with PsA and healthy controls (9). US has been shown to be more sensitive than clinical examination from detecting enthesitis, but the significance of this is currently unclear and there are difficulties with which areas to scan as USS can be time consuming (10).

The first enthesitis index was developed by Mander *et al*. A list of all entheses easily accessible to clinical examination was created and this was tested on 19 patients with AS, which resulted in a measure of 66 entheseal sites graded on a semi-quantitative score from 0 to 3 (0 = no pain, 1 = mild tenderness, 2 = moderate tenderness, and 3 = wince or withdraw) (11). A further study showed correlation of the Mander Enthesitis Index (MEI) with pain and stiffness VAS scales and a reduction in the score with NSAID treatment. There was some variability between different examiners performing the MEI, but intra-observer variability was not formally tested (11). Further validation provided evidence of a correlation between the MEI and other disease activity measures in AS (12). This index has not been used in randomised control trials likely due to burden of administration and concern relating to sites overlapping with fibromyalgia points.

The Maastrict Ankylosing Spondylitis Enthesitis Score (MASES) was developed during the validation of the MEI. During a 2 year period AS patients had an MEI done and the 13 most specific and sensitive sites were chosen to be included in the reduced MASES score with a dichotomous 0/1 score for tenderness. There was correlation between the enthesitis scores and disease activity measures (12). The MASES has not been validated in PsA, though in the International Spondyloarthritis Interobserver Reliability Exercise (INSPIRE) in which a number of enthesitis indices were compared for use in AS or PsA there was moderate intraobserver reliability among PsA patients (ICC 0.56, 95% CI 0.34, 0.82) (13). Data from 24 weeks and 52 weeks in the golimumab PsA trials indicate MASES demonstrates discrimination and responsiveness (14, 15).

More recently, the Spondyloarthritis Research Consortium of Canada (SPARCC) created a new outcome measure for enthesitis in SpA (16) using information from ultrasound and MRI studies in PsA, healthy controls and AS patients. They identified the 16 most frequently affected entheseal sites that could be clinically assessed.(7). Interobserver reliability was good and a substantial correlation was seen between the enthesitis score and other disease activity measures. Generally enthesitis is felt to improve with anti-TNF which was the case using this measure, though the reduction in enthesitis score was not significant after 12 weeks of therapy (16). Reduced versions of the SPARCC enthesitis index using more commonly involved sites showed larger effect sizes and standardised response means. This would be useful in clinical practice as it would take less time but still identify improvement in enthesitis (16).

All of the entheseal outcome measures discussed previously were developed for spondyloarthropathy and validated on patients with AS. The Leeds En-

thesitis Index (LEI) is the only measure developed specifically for PsA. The 6 most commonly involved entheseal sites were identified using a step-wise process (Table II) (17). This index was then compared to other entheseal indices in an open-label longitudinal study. The LEI showed closest correlation with other disease activity measures, a large effect size and the smallest floor effect when compared with the MEI. This low floor effect means that it can identify the majority of patients with enthesitis using just 6 sites, making it far more feasible (17). The LEI has been used in a randomised control study with certolizumab in PsA with significant improvements in the treatment group arms compared to the placebo, indicating the ability of the LEI to demonstrate responsiveness (18). In the INSPIRE study, in patients with PsA, both LEI and SPARCC showed excellent agreement (13).

The other limitation of clinical enthesitis counts is the specificity of the finding of tenderness in these areas. Many of the entheseal points are relatively near to joints and accepted fibromyalgia points, raising the possibility that misclassification could occur. The key to the reliability of these tools in clinical practice is the training provided to assessors in localising the correct points.

Table II. Ehtheseal sites assessed in outcome measures*.

	MASES	SPARCC	LEI
First costochondral	R, L		
Seventh costochondral	R, L		
Supraspinatous insertion		R, L	
Lateral epicondyle humerous		R, L	R, L
Medial epicondyle humerous		R, L	
Posterior superior iliac crest	R, L		
Anterior superios iliac crest	R, L		
Iliac crest	R, L		
Fifth lumbar spinous process	X		
Proximal achilles	R, L	R, L	R, L
Greater trochanter		R, L	
Medical condyle femur			R, L
Lateral condyle femur			
Insertion plantar fascia		R, L	
Quadriceps insertion patella		R, L	
Inferior pole patella		R, L	
Tibial tubercle		R, L	
Estimated time to complete	~2-5 minutes	~2-5 minutes	~ 30 seconds

*MASES: Maastrict Ankylosing Spondylitis Enthesitis Score; SPARCC: Spondyloarthritis Research Consortium of Canada; LEI: Leeds Enthesitis Index; X: single site; R: right; L: left.

Dactylitis

Dactylitis describes a uniform swelling of a digit with inflammation causing a *sausage digit* and is a hallmark feature of PsA and is one of the items used to make a diagnosis of PsA using the CASPAR criteria (1). Dactylitis can be further characterised as acute/tender dactylitis where the digit is tender, often erythematous and warm, or as chronic/sub-acute/non-tender dactylitis where the digit is swollen but non-tender. It has been hypothesised that the chronic form occurs following an episode of acute dactylitis in some patients but this has not been confirmed.

The definition and pathology of dactylitis remains problematic. Studies using imaging have confirmed that physical examination can identify pathology in tender dactylitis (19). However this study only assessed 12 obviously swollen digits and the contralateral normal digits. Therefore it seems likely that in normal clinical practice, there will be some variation between observers resulting in lower agreement particularly in *grey* cases, where digits may be slightly swollen. This was later confirmed by a reliability study performed in Canada. This showed a moderate agreement (kappa 0.57, 95%CI=0.34, 0.82) between 10 experienced observers for number of digits with dactylitis (20). Clinical measures of dactylitis have been used as secondary outcome measures in clinical trials but the majority have used non-validated measures. The simplest measure used is a simple count of dactylitic digits, though some studies have used non-validated physician graded severity which previously has been shown to have poor inter-observer reliability, which adds to the difficulties of devising a measure suitable in clinical practice (21).

The Leeds Dactylitis Instrument was developed in response to this need for a clinical, objective, validated outcome measure for dactylitis (see Figure 2). Based on the evaluation of the median difference in digital circumference between dactylitic digits and control digits dactylitis was defined as an increase in circumference of the digit of more than 10% compared to the contralateral non-affected digit (22). The aim of the LDI is to provide a quantification of both the size and tenderness so that the score can differentiate between tender and non-tender dactylitis. The tenderness scoring can be based on the RAI with tenderness scored from 0-3 (LDI scoring) or can be simplified to a dichotomous score of 0 for non-tender and 1 for tender (LDI basic) (22).

The first study comparing dactylitis outcome measures showed a relatively poor inter-observer reliability for identifying tender dactylitis and a poor agreement on non-tender dactylitis. This was improved significantly by using the LDI scoring system. Inter and intraobserver reliability for the LDI score was good, and was increased further using the LDI basic, suggesting that some of the variability was due to the inaccuracy of grading tenderness (22).

A longitudinal study with 28 patients who were changing treatment was performed to further investigate the use of this clinical tool and to compare it to other measures (tender dactylitis count, all dactylitis count, IMPACT1, LDI, LDI basic). All measures showed a change with treatment after 3 and 6 months. The majority of these correlated with other clinical disease activity measures such as joint counts and VAS for disease activity (23). Only the count of all dactylitic digits performed badly probably due to the inclusion of non-tender dactylitis which may not be thought to represent disease activity.

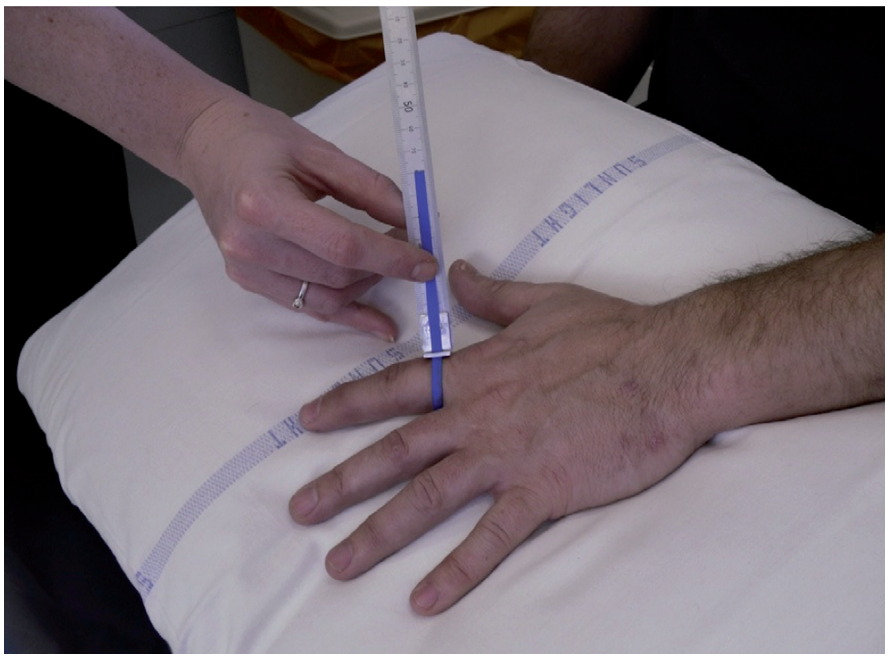

Fig. 2. A dactylitic digit being measured using the dactylometer (30).

A subgroup of patients in the above study also had MRI scans performed at baseline and 6 months to assess the inflammation in the dactylitic digits. Similar to the Olivieri study (19), this showed that clinically tender dactylitic digits had significant MRI abnormalities compared to non-involved digits or non-tender dactylitis. However the correlation between the level of inflammation on MRI and clinical evaluation was moderate at best (0.37 for LDI local score and MRI score) (24).

Although the LDI and LDI basic measures do take longer to perform, particularly if multiple digits are involved, these measures perform better in terms of both truth and discrimination when considering the tool in the context of the OMERACT filter (23). Thus, it is the most validated clinical outcome measure available for dactylitis. In a randomised control trial where dactylitis was a secondary outcome the LDI was able to identify improvements in dactylitis in the treatment groups (18).

Composite measures of psoriatic arthritis involving enthesitis and dactylitis measurements

Given the complexity of PsA and the multiple areas that can be affected composite scores may be useful in providing a tool that can be used both in trials and in the clinical setting, this is currently an area that is on the research agenda for GRAPPA.

The Composite Psoriatic Disease Activity Index (CPDAI) assesses 5 domains (joints, skin, entheseal, dactylitis, and spinal manifestations) with a measure of disease activity and impact on the patient for each domain (25). This was recently compared to the Disease activity in Psoriatic Arthritis (DAPSA) (26) in data sets from a randomised control trial using etanercept.Both were effective in determining treatment response however CPDAI could distinguish response between the two etanercept doses suggesting it may be a more sensitive tool (27). More recently the GRACE project for development of psoriatic arthritis indices led to the Psoriatic Arthritis Disease Activity Score (PASDAS) which measures physician and patient VAS, swollen and tender joint count, CRP, enthesitis, dactylitis count, and the physician component summary of the short-form 36 (28). Initial comparisons with other composite measures such as the CPDAI suggested the PASDAS was better able to discriminate between high and low disease activity. This was further compared using data from a golimumab study and the PASDAS was better able to distinguish treatment effect (29)

Research agenda

- Further research is needed in enthesitis to investigate the usefulness and validity of using these scoring systems in clinical practice as well as clinical trials. Further correlation with imaging is likely to be interesting in future studies.
- Further validation of the composite indices will indicate if these may be useful in practice as well as clinical trials.
- Further evaluation of dactylitis measures in clinical practice and whether using a specific outcome measure is more useful than using a tender dactylitis count.

Conclusion

There has been much progress in outcome measures in PsA in the last decade. There are now validated scoring systems for enthesitis and dactylitis along with composite measures that include these elements. Many are used in clinical trials and have shown good sensitivity to change, however their use in clinics may be limited in part by time and lack of knowledge and education about these tools. Studies of enthesitis have shown a discord between findings on MRI or USS and clinical assessment, however whether this is clinically relevant needs to be further investigated. Though some of the entheseal tools are quick many assessment points are near to joints and may be positive if there is active joint inflammation or chronic damage, reducing sensitivity. Dactylitis assessments such as the LDI are likely useful in research trials, however their use in clinical practice may be limited due to time constraints. Many tools have shown to be strongly associated with other measures of disease activity such as VAS pain and stiffness scores, which identifies the question of the additional benefits of specific measures. In busy clinical practice, generic measures such as VAS scales for disease activity and measures of disease impact such as the HAQ can be very useful, but in such a heterogenous disease physicians assessments should consider all aspects of disease to ensure that a holistic approach to treatment is taken. It is likely that in clinical practice composite

measures could have great benefit and more needs to done to further investigate their use in long-term observational cohorts which would indicate which ones may be useful in clinical practice.

References

1. TAYLOR W, GLADMAN D, HELLIWELL P *et al*.: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665-73.
2. COATES LC, CONAGHAN PG, EMERY P *et al*.: Sensitivity and specificity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. A*rthritis Rheum* 2012; 64: 3150-5.
3. GLADMAN DD, MEASE PJ, STRAND V *et al*.: Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol* 2007; 34: 1167-70.
4. MCGONAGLE D, LORIES RJ, TAN AL, BENJAMIN M: The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. *Arthritis Rheum* 2007; 56: 2482-91.
5. GLADMAN DD, CHANDRAN V: Observational cohort studies: lessons learnt from the University of Toronto Psoriatic Arthritis Program. *Rheumatology* (Oxford) 2011; 50: 25-31.
6. MARZO-ORTEGA H, MCGONAGLE D, O'CONNOR P, EMERY P.: Efficacy of etanercept in the treatment of the entheseal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study. [see comment]. *Arthritis Rheum* 2001; 44: 2112-7.
7. D'AGOSTINO MA, SAID-NAHAL R, HACQUARD-BOUDER C, BRASSEUR JL, DOUGADOS M, BREBAN M: Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum* 2003; 48: 523-33.
8. MCQUEEN FM, GAO A, OSTERGAARD M *et al*.: High-grade MRI bone oedema is common within the surgical field in rheumatoid arthritis patients undergoing joint replacement and is associated with osteitis in subchondral bone. *Ann Rheum Dis* 2007; 66: 1581-7.
9. EDER L, JAYAKAR J, THAVANESWARAN A *et al*.: Is the MAdrid Sonographic Enthesitis Index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls? *J Rheumatol* 2014; 41: 466-72.
10. BALINT PV, KANE D, WILSON H, MCINNES IB, STURROCK RD *et al*.: Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002; 61: 905-10.
11. MANDER M, SIMPSON JM, MCLELLAN A, WALKER D, GOODACRE JA, DICK WC: Studies with an enthesis index as a method of clinical assessment in ankylosing spondylitis. *Ann Rheum Dis* 1987; 46: 197-202.
12. HEUFT-DORENBOSCH L, SPOORENBERG A, VAN TUBERGEN A *et al*.: Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis* 2003; 62: 127-32.
13. GLADMAN DD, INMAN RD, COOK RJ *et al*.: International spondyloarthritis interobserver reliability exercise--the INSPIRE study: II. Assessment of peripheral joints, enthesitis, and dactylitis. *J Rheumatol* 2007; 34: 1740-5.
14. KAVANAUGH A, MCINNES I, MEASE P, *et al*.: Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; 60: 976-86.
15. KAVANAUGH A, MEASE P: Treatment of psoriatic arthritis with tumor necrosis factor inhibitors: longer-term outcomes including enthesitis and dactylitis with golimumab treatment in the Longterm Extension of a Randomized, Placebo-controlled Study (GO-REVEAL). *J Rheumatol* 2012; 89 (Suppl.): 90-3.
16. MAKSYMOWYCH WP, MALLON C, MORROW S *et al*.: Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. *Ann Rheum Dis* 2009; 68: 948-53.
17. HEALY PJ, HELLIWELL PS: Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. *Arthritis Rheum* 2008; 59: 686-91.
18. MEASE PJ, FLEISCHMANN R, DEODHAR AA *et al*.: Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; 73: 48-55.
19. OLIVIERI I, BAROZZI L, FAVARO L *et al*.: Dactylitis in patients with seronegative spondylarthropathy. Assessment by ultrasonography and magnetic resonance imaging. *Arthritis Rheum* 1996; 39: 1524-8.
20. GLADMAN DD, COOK RJ, SCHENTAG C *et al*.: The clinical assessment of patients with psoriatic arthritis: results of a reliability study of the spondyloarthritis research consortium of Canada. *J Rheumatol* 2004; 31: 1126-31.
21. FUCHS HA, BROOKS RH, CALLAHAN LF, PINCUS T: A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. *Arthritis Rheum* 1989; 32: 531-7.
22. HELLIWELL PS, FIRTH J, IBRAHIM GH, MELSOM RD, SHAH I, TURNER DE: Development of an assessment tool for dactylitis in patients with psoriatic arthritis. *J Rheumatol* 2005; 32: 1745-50.
23. HEALY PJ, HELLIWELL PS: Measuring dactylitis in clinical trials: which is the best instrument to use? *J Rheumatol* 2007; 34: 1302-6.
24. HEALY P, GROVES C, CHANDRAMOHAN M, HELLIWELL PS: MRI changes in psoriatic dactylitis - extent of pathology, relationship to tenderness and correlation with clinical indices. *Rheumatology* (Oxford) 2008; 47: 92-5.
25. MUMTAZ A, GALLAGHER P, KIRBY B *et al*.: Development of a preliminary composite disease activity index in psoriatic arthritis. *Ann Rheum Dis* 2011; 70: 272-7.
26. EBERL G, STUDNICKA-BENKE A, HITZELHAMMER H, GSCHNAIT F, SMOLEN JS: Development of a disease activity index for the assessment of reactive arthritis (DAREA). *Rheumatology* (Oxford) 2000; 39: 148-55.
27. FITZGERALD O, HELLIWELL P, MEASE P *et al*.: Application of composite disease activity scores in psoriatic arthritis to the PRESTA data set. *Ann Rheum Dis* 2012; 71: 358-62.
28. HELLIWELL PS, FITZGERALD O, MEASE PJ: Development of composite measures for psoriatic arthritis: a report from the GRAPPA 2010 annual meeting. *J Rheumatol* 2012; 39: 398-403.
29. HELLIWELL PS, KAVANAUGH A: Comparison of composite measures of disease activity in psoriatic arthritis using data from an interventional study with golimumab. *Arthritis Care Res* (Hoboken) 2014; 66: 749-56.
30. COATES LC, HELLIWELL PS: Disease measurement--enthesitis, skin, nails, spine and dactylitis. *Best Pract Res Clin Rheumatol* 2010; 24: 659-70.