Measuring Dactylitis in Clinical Trials: Which Is the Best Instrument to Use?

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ABSTRACT. ***Objective.*** Until recently there were no validated tools to assess and measure dactylitis, but a quasi-objective measure of dactylitis (the Leeds Dactylitis Index, LDI, and a simplified version, the LDI basic) has now been developed. We undertook an open-label observational trial to test the responsiveness of the LDI and other measures previously used in clinical trials.

Methods. Twenty-eight patients with a diagnosis of psoriatic arthritis (as defined by the new ClASsification criteria for Psoriatic ARthritis, CASPAR) and active disease including new-onset dactylitis were enrolled. The patients underwent clinical assessment at baseline, 2 weeks, and 1, 3 and 6 months after change of disease modifying therapy, usually to methotrexate. Comparator dactylitis tools were taken from the literature and denoted IMPACT1 (Infliximab Multinational Psoriatic Arthritis Controlled Trial), Clegg, and Salvarani.

Results. All 5 measures of dactylitis showed significant change from baseline and a large effect size (effect sizes first to last clinic visit: LDI 0.99, LDI basic 0.9, IMPACT1 1.63, Clegg 0.77, Salvarani 1.27). The correlation with clinical measures was strongest for the IMPACT1 score, but all the indices except Clegg had a significant positive relationship with tender joint counts, swollen joint counts, Disease Activity Score 28, and patient and physician global measures. When considering the 5 measures of dactylitis within the Outcome Measures in Rheumatology [Clinical Trials] filter, the LDI and the LDI basic showed the best overall fit for the domains of truth, discrimination, and feasibility.

Conclusion. With the important points in its development examined, the LDI is now ready to be used in larger randomized controlled trials both as an outcome measure and to allow further assessment of its utility. (First Release Feb 15 2007; J Rheumatol 2007;34:1302–6)

Key Indexing Terms:
PSORIATIC ARTHRITIS DACTYLITIS MEASUREMENT

Dactylitis is a hallmark feature of psoriatic arthritis (PsA) occuring in 16%–24% of reported cases. It has been defined as "uniform swelling such that the soft tissues between the metacarpophalangeal and proximal interphalangeal, proximal and distal interphalangeal, and/or distal interphalangeal joint and digital tuft are diffusely swollen to the extent that the actual joint swelling can no longer be independently recognized"[1]. The importance of dactylitis in PsA is further supported by its inclusion in the classification criteria recently developed by an international group[2]. Dactylitis appears to have prognostic significance, as it is associated with more aggressive disease in affected digits[3].

While dactylitis has been recognized as important, treatment trials specifically aimed at dactylitis have not been conducted. However, dactylitis has been included as one of the secondary outcomes in several trials, although a variety of unvalidated measures have been used. This may relate to lack of both a standardized definition and the ability of the measures to respond to change. Clegg, *et al* used a simple count of digits with dactylitis, both tender and nontender, as determined by the reviewing physician[4]. Salvarani, *et al* used a count of dactylitic digits that were tender[5]. The TOPAS study graded dactylitis 1–4 on a physician-judged level of severity, but the concept of severity was not explained[6]. Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT1) used a 0–3 scale of physician-rated severity for each affected digit, and summed the results with a maximum of 60[7]. IMPACT2 used a simple tender digit count, but reported the percentage of patients who had dactylitis and the percentage that had a change in their dactylitis[8].

Recently a more objective measure (Leeds Dactylitis Index, LDI) has been developed[9]. The LDI measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot: a minimum difference of 10% is used to define a dactylitic digit (this represented the mean difference recorded by 5 observers in the above study). If ipsilateral and contralateral digits are thought to be involved, a table of normative values is used to provide the comparison. The ratio of circumference is multiplied by a tenderness score, originally based on the Ritchie index (graded

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0–3), but a later modification amended this to a binary score (0 for nontender, 1 for tender — this later modification is referred to as the LDI basic). Tenderness is assessed in the area between the joints using the maximum recorded. The results from each digit with dactylitis are then summed to produce a final score. The LDI reliability is good, with inter- and intraobserver intraclass correlation coefficient (ICC) reported as 0.9 and 0.84, respectively. As this tool still requires an assessment of responsiveness, a prospective open-label observational study was undertaken. We also evaluated the responsiveness of the other measures of dactylitis.

MATERIALS AND METHODS

The study took place in a secondary care setting in Bradford NHS Trust in West Yorkshire, UK. Approval was given by the local ethics committee. Patients over the age of 18 years fulfilling the criteria for PsA as described by the CASPAR study group[2] with active disease (≥ 3 tender and/or ≥ 3 swollen joints based on a 78 tender and 76 swollen joint count) were included. For the purposes of this study dactylitis was counted as one active joint (tender and swollen) if the digit was tender to pressure, with a maximum of one dactylitic digit to count. Any patient who had recent (3 months) changes in disease modifying antirheumatic therapy or recent (3 months) injection of corticosteroids into the dactylitic digit was excluded. Patients with active disease, as defined above, who were intolerant or unresponsive to their current disease modifying therapies, or had not yet begun disease modifying therapy and presented with dactylitis, were invited to participate as they attended outpatient rheumatology clinics. A full study information sheet and written consent form was provided. Those who provided written consent to participate underwent an initial assessment of joint and skin disease. A letter confirming their inclusion in the study was sent to their general practitioner in addition to standard clinic letters regarding changes to drug therapy. Drug therapy was chosen by the managing clinician as considered appropriate. Patients underwent clinical assessments at baseline (start of new drug therapy), 2 weeks, and 1, 3 and 6 months. This followup procedure was more intensive than normal but the care of the patient, and the choice of drug, was no different from normal clinical care.

Clinical assessment included the following instruments; LDI (as described), the LDI basic, Clegg, Salvarani, and IMPACT1[3-6]. In addition, the Mander Enthesitis Index (MEI)[10], Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)[11], Psoriasis Area and Severity Index (PASI)[12], a 78-joint count (78 tender and 76 swollen), a measure of acute phase response (C-reactive protein), the British Health Assessment Questionnaire (HAQ)[13], the Psoriatic Quality of Life tool (PsQoL)[14], and a patient and physician global assessment using both a 10 cm visual analog scale (VAS) and a Likert scale were employed. Together these measurements facilitate calculation of the disease activity scores Psoriatic Arthritis Response Criteria (PsARC)[4], American College of Rheumatology (ACR)20[15], and Disease Activity Score (DAS)28[16]. Further validation of the ACR20 and DAS28 in PsA is required, but preliminary data suggest that they may be useful in polyarticular PsA[17].

Patients were monitored for serious adverse events as per usual clinical practice via clinical examination and routine laboratory monitoring, including full blood count and differential white count, urea, electrolytes, liver function tests, and acute phase response. Rheumatoid factor was measured at the start of the study. Antinuclear antibodies were measured in those receiving biologic therapy.

Statistics. The data were examined using SPSS12. Descriptive statistics are mean values. The analysis of change was examined with the Wilcoxon signed-rank test and Cohen's d was used to calculate effect size[18]. Spearman's rho was used to correlate clinical features with the various outcomes measures.

RESULTS

The demographics and baseline variables are described in Table 1. The sex ratio was equal, with a mean age of 46.5 years. Disease duration ranged from 9 months to 37 years (mean 10.5 yrs). The HAQ, tender joint count (TJC), swollen joint count (SJC), and physician and patient global VAS along with the DAS28 indicate active disease with significant impact. Methotrexate was initiated in 19 patients, leflunomide in 4, etanercept in 4, and hydroxychloroquine in 1.

Table 1. Baseline characteristics.

Variable	Mean (SD)	Range
Sex M:F	14:14	
Age, yrs	46.5 (10.5)	24–70
Disease duration, yrs	10.5 (11.3)	0.8–37
CRP, mg, normal < 10	15.3 (13)	5–51
HAQ	1.4 (0.8)	0–2.9
Tender joint count	16.3 (12.5)	1–47
Swollen joint count	8.9 (4.3)	1–20
Physician global VAS	51.3 (21.1)	15–89
Patient global VAS	56.2 (20.6)	23–100
DAS28	4.3 (1.0)	2.2–6.7

VAS: visual analog scale; DAS28: Disease Activity Score 28 joints; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein.

The outcomes for the various dactylitis measures can be seen in Table 2. There is a significant change at 3 and 6 months for all the measures ($p < 0.01$). This is shown in Figure 1. The measures all show a large effect size (data given in the legend within Figure 1 and in Table 2) for the treatments used. Patients showed a good response to treatment with acceptable PsARC and ACR20 responses at both 3 and 6 months. The DAS28 indicates a good response at 3 months and moderate response at 6 months. These results are shown in Table 3. The DAS28 changes were significantly different from baseline. These results are encouraging given the mix of therapies dominated by methotrexate and suggest better results might be obtained with biological therapies.

The correlation matrix using the dactylitis indices on one hand and other clinical and laboratory variables on the other is given in Table 4. All the indices except Clegg show a relationship with TJC, SJC, DAS28, and patient and physician global VAS. There was no correlation at any of the timepoints with CRP and HAQ, while only the IMPACT1 score was associated with the patient pain VAS. The strength of the correlation, a marker of external validity, was best overall for the

Table 2. Outcomes for dactylitis measures.

Index	Outcome, mean (SD) [effect size]		
	Baseline	3 Mo*	6 Mo*
LDI	58.5 (47.9)	27.4 (42.51)	16.5 (38.5) [0.99]
LDI basic	29.4 (19.8)	16.3 (23.6)	11.3 (21.8) [0.9]
IMPACT1	3.2 (1.6)	1.2 (1.4)	0.7 (1.5) [1.63]
Clegg[4]	2.2 (1.1)	1.5 (1.4)	1.1 (1.2) [0.77]
Salvarani[5]	1.9 (0.9)	0.8 (0.9)	0.6 (1.1) [1.27]

* All results $p < 0.01$. LDI: Leeds Dactylitis Index; IMPACT1: Infliximab Multinational Psoriatic Arthritis Controlled Trial.

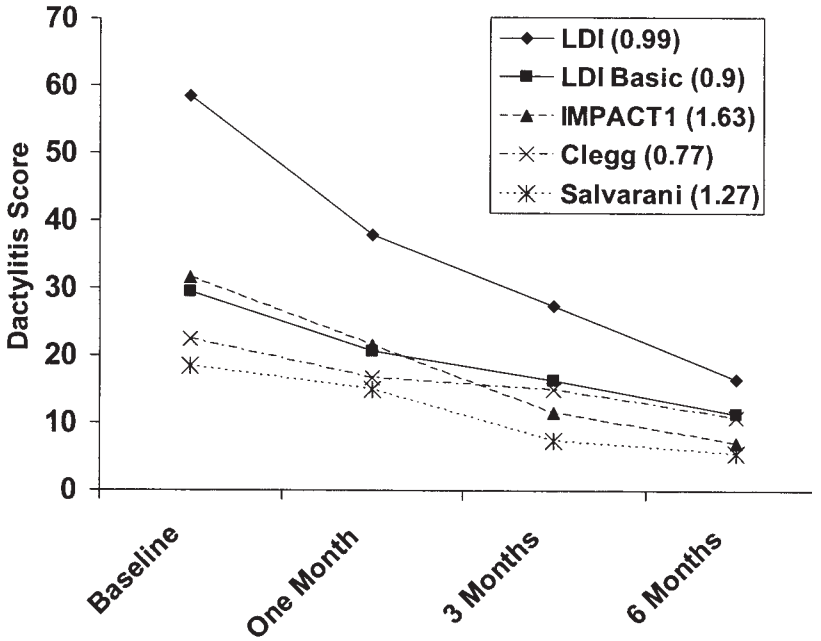

Figure 1. Response to treatment using the 5 different dactylitis tools. The effect size, baseline to final assessment, is given in the legend. IMPACT, Clegg, and Salvarani scores multiplied by 10.

IMPACT1 tool, but there was little difference between the IMPACT1 and LDI coefficients.

DISCUSSION

Our data show that all the available measures for dactylitis have a significant response to change with a large effect size. These results suggest that any of the measures could be used to measure response to change in a trial considering dactylitis in PsA.

The correlations with standard outcome measures such as TJC, SJC, patient global VAS, and DAS28 provide external validity for the LDI, LDI basic, IMPACT1, and Salvarani scores. This suggests that they are relevant to the disease process being investigated and are hence likely to improve as the disease control improves. The Clegg score does not perform as well in the correlation matrix. This is likely due to the inclusion of nontender dactylitis in the score.

In order to be used as an outcome measure a tool needs to fulfil a number of requirements best encapsulated by the Outcome Measures in Rheumatology [Clinical Trials] (OMERACT) filter domains of truth (validity), discrimination (reproducibility and responsiveness), and feasibility. The OMERACT filter is intended to help evaluate the overall usefulness of an outcome measure. While it requires an element

Table 3. Composite disease outcomes.

Measure	Outcome		
	Baseline	3 Mo	6 Mo
PsARC, %	—	54	61
ACR20, %	—	50	43
DAS28 score	4.3	3.0*	3.4*

* $p < 0.01$. PsARC: Psoriatic Arthritis Response Criteria; ACR: American College of Rheumatology.

Table 4. Correlation matrix for dactylitis indices and clinical measures. Figures represent Spearman rho correlation coefficients for each of the dactylitis tools at each assessment over the study (n = 140).

Index	Clinical Measure							
	CRP	Physician Global VAS	TJC	SJC	HAQ	Patient Pain VAS	Patient Global VAS	DAS28
LDI	0.093	0.374**	0.488**	0.505**	-0.032	0.195	0.298**	0..296**
LDI basic	0.071	0.320**	0.431**	0.493**	-0.107	0.133	0.241*	0.242*
IMPACT1	0.135	0.408**	0.558**	0.569**	0.012	0.227*	0.303**	0.393**
Clegg[4]	0.198	0.179	0.220**	0.637**	-0.191	0.011	0.000	0.020
Salvarani[5]	0.185	0.347**	0.495**	0.534**	-0.028	0.091	0.216*	0.319**

CRP: C-reactive protein; VAS: visual analog scale; TJC: tender joint count; SJC: swollen joint count; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score 28 joints. * $p < 0.05$, ** $p < 0.01$.

of informed judgment to be effective, it provides a good framework to allow that judgment to be made as objectively as possible.

Truth. The underlying pathophysiology of dactylitis has been difficult to determine in the spondyloarthropathies. Synovitis, tenosynovitis, and enthesitis have been reported. Most of the information comes from the magnetic resonance imaging (MRI) studies of Olivieri, *et al*[19-24]. This group described tenosynovitis as universal, with synovitis in 0–27% and occasional peritendinous soft tissue edema. The ultrasound scan study from Kane, *et al* confirmed almost universal tenosynovitis, but noted synovitis in 52% and frequent subcutaneous edema that could not be quantified[25]. Histopathological studies in mice also support the concept of subcutaneous edema and tenosynovitis[26].

This understanding of the pathophysiology suggests that a measure encompassing edema or swelling might be a more accurate, or true, indicator of disease. All the measures except LDI and LDI basic use a physician-determined presence or absence of dactylitis. While this may be accurate for grossly swollen digits, it is possible that more subtle changes are both included and excluded inappropriately. An objective measure, taking swelling into account, with a formal numerical definition permits a reliable assessment and comparison across different centers. By considering the circumference of the involved digit, in conjunction with tenderness, the LDI and LDI basic are more directly related to the underlying pathophysiology.

Discrimination. All the measures of dactylitis we tested have shown a good response to change, suggesting they may be appropriate for assessing the effect of treatment. While all the measures have been used in clinical scenarios, the reliability and repeatability of the measures have only been assessed for the LDI and LDI basic[9]. A further area that may cause variability in assessment is the use of physician-graded pain or severity. It has been shown that the Ritchie index is not a reliable, repeatable measure of joint pain in rheumatoid arthritis[27] and so a simple binary outcome is preferred. In this respect the Salvarani score and LDI basic would be the recommended measures.

Feasibility. If a measure is time-consuming or requires extra resources it will not be used no matter how truthful or discriminatory it is. It should be noted that an assessment of dactylitis is an additional measurement in any clinical trial and will require extra time regardless of how it is measured. However, if dactylitis is to be assessed, then the LDI takes roughly 1 minute to assess 3 paired digits. The other tools would require the normal time taken to assess tender and swollen joints. The LDI also requires a tool to measure digital circumference (an appropriate tool is available from http://rehaboutlet.com, Miami, FL, USA).

One of the problems with the definition of dactylitis is that a chronic nontender form exists in patients with PsA. It is unknown whether this is simply resolving tender dactylitis or a different process, as we have little data on the nontender state. The article by Brockbank, *et al*[3] suggests worse outcomes for tender dactylitis and so consideration of this alone may be appropriate. Although the LDI allows a numerical definition of dactylitis, the current position is that the zero multiplier excludes nontender digits from the total score, so some modification would be necessary.

The main limitation of our study is the small sample size, although this is the largest group with dactylitis to be followed longitudinally. Specifically, this small study has provided useful pilot data on which to base power calculations for a larger, randomized controlled trial should dactylitis be considered to be the main outcome measure.

Dactylitis has classification and prognostic importance. A number of dactylitis measures showed a good response to change and may be appropriate for clinical trials. When considering the 5 measures of dactylitis within the OMERACT filter, the LDI and LDI basic show the best overall fit for the domains of truth, discrimination, and feasibility. With most of the important points in its development examined, the LDI is now ready to be used in larger randomized controlled trials, both as an outcome measure and to allow further assessment of its utility.

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