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**How are enthesitis, dactylitis and nail involvement measured and reported in recent clinical trials of Psoriatic Arthritis (PsA)? A systematic literature review**

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Whilst enthesitis, dactylitis and nail involvement are recognized as important outcomes of psoriatic arthritis (PsA) in the core set of domains in PsA,[1,2] it is still unclear how these outcomes should best be measured.[1,2] We systematically reviewed the instruments and the cutoffs used to report state or improvement, for enthesitis, dactylitis and nail involvement in recent randomised controlled trials (RCTs) in PsA.

A systematic literature review of RCTs on any pharmacological intervention in patients with PsA was conducted to inform the EULAR recommendations for the management of PsA, by searching Medline, Embase and Cochrane datasets for the period 2010-2015.[3,4] Only published papers and only results of the placebo-controlled phases were analysed. The presence and type of all outcome measures reflecting enthesitis, dactylitis and nail involvement were collected. Cutoffs used for each measure (either as state or change, absolute or relative) were also collected. The proportion of trials in which each of the cutoffs for each measure was reported was calculated.

Of 2,278 articles screened, 14 trials met the inclusion criteria: 4 (29%) reported on non-biologic drugs (included targeted synthetic DMARDs, 1 trial), 5 (36%) on tumor necrosis factor inhibitors, 4 (29%) on other biologic modes of action and there was one strategy trial. The trials included a total of 4,744 patients. Four of the trials (29%) did not report any outcome on any of the 3 domains of interest (Table 1). Enthesitis and dactylitis outcomes were reported in the remaining 10 trials, while nail involvement was only reported in 3 trials (21%). These three outcomes have been measured in several different ways, none of which having been used in more than 3 trials (21%), and the majority of them was actually employed in only 1 (7%) or 2 (14%) trials. Different instruments have been used, different cutoffs and different statistics reported (e.g. mean and median improvement or resolution of the outcome, e.g. enthesitis score of zero) (Table 1). It was often the case that the same outcome measure was used (e.g. the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)), but then reported in such different ways (e.g. percentage of change, percentage $\geq$ 1, percentage of improvement in one tendon/ligament, etc), that the potential uniformity in the measures used got diluted (Table 1). There was also heterogeneity in the timing of report of the outcome measures across trials.

In summary, there is substantial lack of uniformity in the measurement of enthesitis, dactylitis and nail involvement in recent clinical trials of PsA. A similar lack of uniformity had previously been described for patient reported outcomes in PsA,[5,6] and in what concerns enthesitis, dactylitis and nail involvement measurement is the heterogeneity even larger. This relates to both the instruments used and the evaluation and interpretation of the results. An important aspect that requires attention are the ways in which the data are reported, namely the cutoffs chosen or the different statistics reported, which make the heterogeneity larger, even when one single outcome measure (see the example of MASES) is being used. Assessment of dactylitis and enthesitis needs further development taking both their resolution and appearance into account. Another methodological aspect deserving attention is the fact that these outcomes are actually only investigated in patients with active involvement at baseline, which violates the principle of intention to treat analysis. Consensus is necessary and more elegant solutions should be considered. An update of the PsA Core Set of domains has just been published, however, without any indication of the instruments and cutoffs to be used.[2] Harmonization of measures to be used in trials and possibly also clinical practice is desirable to allow for optimal assessment and better comparability of the efficacy of interventions.

Table 1 - Outcome measures used in 14 recent trials in PsA

| Manifestation    | Outcome measure                                  | Level of measurement                                       | N (%)   |
|------------------|--|--|---------|
| Any              | No manifestation reported                        |  | 4 (29%) |
| Enthesitis       | Absolute change in enthesitis score              | Change (mean) in Leeds enthesitis index                    | 2 (14%) |
|                  |  | Change (mean) in PsA modified MASES                        | 3 (21%) |
|                  |  | Change (median) in MASES                                   | 1 (7%)  |
|                  | Relative change (%) in enthesitis score          | % change in MASES  | 2 (14%) |
|                  | Proportion of patients with enthesitis           | MASES (0-13) $\geq$ 1                                      | 2 (14%) |
|                  | Proportion of patients with change               | % of patients with improvement in $\geq$ 1 tendon/ligament | 1 (7%)  |
|                  | Resolution of enthesitis                         | MASES =0 (0-13)  | 1 (7%)  |
|                  |  | Leeds enthesitis index =0 (0-6)                            | 1 (7%)  |
|                  |  | Enthesitis score =0 (0-4)*                                 | 1 (7%)  |
| Dactylitis       | Absolute change in dactylitis score              | Change (mean) in Dactylitis score (0-20)§                  | 2 (14%) |
|                  |  | Change (median) in Dactylitis score (0-20)                 | 1 (7%)  |
|                  |  | Change (median) in Leeds dactylitis index (0-60)           | 2 (14%) |
|                  |  | Change (mean) in Leeds dactylitis index (0-60)             | 2 (14%) |
|                  | Relative change (%) in dactylitis score          | % change in Leeds dactylitis index (0-60)                  | 3 (21%) |
|                  | Proportion of patients with dactylitis           | Leeds dactylitis index (0-60) $\geq$ 1                     | 2 (14%) |
|                  | Resolution of dactylitis                         | Dactylitis score =0 (0-20)                                 | 3 (21%) |
| Nail involvement | Absolute change in score of nail involvement     | Change (mean) in modified Nail Psoriasis Severity Index    | 1 (7%)  |
|                  |  | Change (median) in modified Nail Psoriasis Severity Index  | 1 (7%)  |
|                  |  | Change (median) in Nail Psoriasis Severity Index           | 1 (7%)  |
|                  | Relative change (%) in score of nail involvement | % change in Nail Psoriasis Severity Index                  | 1 (7%)  |

PsA: psoriatic arthritis; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score

\* Enthesitis score: 4-point enthesitis index to measure the presence (score of 1) or absence (score of 0) of tenderness at the lateral epicondyle humerus (left and right) and proximal achilles (left and right)

§ Dactylitis score: score of 1 for the presence of dactylitis and 0 for the absence in each digit (n=20), for an overall score ranging from 0 to 20

**Competing interests:** None declared

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