

Editorial

# How Should We Measure Peripheral Spondyloarthritis?

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Spondyloarthritis (SpA) is recognized as an overarching spectrum of disease characterized by axial SpA (axSpA), peripheral arthritis, enthesitis, and dactylitis. Despite significant overlap, patients are often characterized as having predominantly peripheral or axial involvement. There are advantages to the separate assessment of peripheral and axial disease, particularly in the randomized clinical trial (RCT) setting, in trying to understand the differential effectiveness of novel biologic and targeted synthetic drugs on the peripheral and axial skeleton. While some diagnoses within the SpA concept have attracted increasing research over recent decades, it seems that peripheral SpA (pSpA; excluding psoriatic arthritis [PsA]) still lags behind.

Peripheral SpA, as defined by the Assessment of Spondyloarthritis international Society (ASAS) criteria, allows a diagnosis in patients with peripheral arthritis alongside other features of SpA.<sup>1</sup> This encompasses PsA but also inflammatory bowel disease–related arthritis, reactive arthritis, and undifferentiated pSpA, representing a diverse group of patients. To date, there have been large numbers of observational and treatment trials in PsA, but there are relatively few in the other forms of pSpA.

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The aim of the publication of these classification criteria was to support future research into this group.

However, in addition to classifying the condition, valid outcome measures are required to examine disease activity, response, and impact in pSpA in the RCT and clinical practice settings. The only large RCT of treatment for nonpsoriatic pSpA to date has been the ABILITY-2 study, which compared adalimumab (ADA) vs placebo.<sup>2</sup> This study used the ASAS criteria for inclusion but also excluded patients with predominant axial disease or PsA, as studies of ADA in these populations had already been completed.

In this study,<sup>2</sup> due to a lack of validated outcome measures addressing arthritis, enthesitis, and dactylitis in this population, a novel composite efficacy outcome measure was designed: the Peripheral SpA Response Criteria (PSpARC40). The PSpARC40 is defined as  $\geq 40\%$  improvement ( $\geq 20$ -mm absolute improvement) in the patient global and pain visual analog scale scores, and  $\geq 40\%$  improvement in one of the following: (1) peripheral joint count; (2) total enthesitis count; or (3) dactylitis count.<sup>2</sup> While this study met its primary outcome of PSpARC40 at Week 12 for ADA compared to placebo, no other validation data are published on this outcome. Interestingly, the trial cohort has attracted attention from researchers as there are few large studies in nonpsoriatic pSpA, and subsequent papers have looked at the validation of “borrowed” outcome measures including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), American College of Rheumatology outcomes, and minimal disease activity as used in PsA.<sup>3,4</sup> However, trial cohorts are never reflective of the more heterogenous real-world populations and so further research in additional real-world datasets in pSpA are needed.

The study by Beckers et al<sup>5</sup> in this edition of *The Journal of Rheumatology* analyzed 3 different composite measures in pSpA, with a focus on examining concurrent validity in the clinical practice setting. This represents a step forward toward validation of outcome measures in pSpA that could support future research, and is strengthened with the use of data from a real-world dataset.

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The study used data from a Dutch SpA registry and focused on 304 patients with pSpA having treatment in routine clinical practice. The study included data on the Disease Activity in PsA (DAPSA), PsA Disease Activity Score (PASDAS), and ASDAS. All these measures correlated well with individual measures of disease activity or impact such as patient/physician global scores and quality of life measures. The ASDAS performed well despite the focus on peripheral SpA rather than axial symptoms, although this is in keeping with previous studies of BASDAI and ASDAS in PsA populations.<sup>6,7</sup> The DAPSA and PASDAS, which were designed for PsA, also performed well, although the proportion of patients classified with active disease activity (moderate–high disease) by the DAPSA was a lot lower than the other measures. This may be because the score is proportional to the tender and swollen joint counts, which may not accurately reflect disease in a predominantly oligoarticular disease.

Unfortunately, as this study<sup>5</sup> was reliant on real-world data collection within the clinic, quite a high number of patients had missing data, particularly for the DAPSA and PASDAS. The other key limitation is that because most patients with pSpA have PsA, this study includes a limited number of patients with nonpsoriatic pSpA (82 of 304 patients), where data are particularly needed.

One of the widely recognized challenges in the pSpA field is the heterogeneous nature of disease. For example, pSpA could encompass a patient with PsA and asymptomatic axial disease, and a patient with nonpsoriatic pSpA monoarthritis. The DAPSA and PASDAS were developed for the purpose of assessing peripheral joint involvement in PsA, whereas the ASDAS was developed to assess disease activity in axSpA. As Beckers et al highlight, a composite measure that includes psoriasis (PsO) may not be appropriate in a patient without PsO.<sup>5</sup> The same concern could apply to those with PsA and no axial involvement where instruments such as ASDAS may not be appropriate. In both instances, the instrument may lack face validity. A further challenge is the influence of axSpA and pSpA on an instrument and for this reason, subanalyses are often made on modified versions of the BASDAI and ASDAS to try and separate out change in axial and peripheral symptoms. The question that arises is whether we should be repurposing outcome measures developed for subtypes of axSpA to apply to the axSpA population as a whole, or whether some subtypes are sufficiently different and prevalent to justify dedicated outcome measures.

The same dilemma of lumping or splitting exists with respect to axial involvement in PsA, where there the exact nature of axial involvement in PsA is yet to be determined. To that end, a collaboration between the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and ASAS has been formed to study axial PsA in a multinational, multicenter cross-sectional study. The Axial Involvement in Psoriatic Arthritis Cohort (AXIS) study aims to enroll 400 patients to determine the prevalence and phenotype of axial PsA using imaging, clinical, and laboratory assessments.<sup>8</sup> The collaboration between ASAS and GRAPPA in the AXIS study could be a future forum to validate or develop a novel composite instrument for use across the spectrum of pSpA.

The Outcome Measures in Rheumatology (OMERACT) method for selecting an assessment can be helpful when considering the relative merits of an assessment tool. The instrument selection process starts with understanding what you are trying to measure, including the domains of disease and context such as RCTs, observational studies, or clinical practice, where the requirements of an instrument will vary. The next steps OMERACT recommends are identification of candidate instruments, determining domain match and feasibility, narrowing the field, and synthesizing (and generating) evidence, before final consensus. In its current form, the entire OMERACT instrument selection process must be repeated separately for RCTs, observational studies, and clinical practice. There is certainly a need for a coordinated approach to the assessment of pSpA in research and clinical practice settings to improve clinical integration and reporting of RCTs. The requirements of a measurement instrument may differ in each setting. For example, in the RCT setting, discrimination is a high priority whereas in observational research and routine clinical practice, feasibility may be a priority. In judging each of the instruments tested by Beckers et al<sup>5</sup> through the OMERACT lens, there are encouraging results with respect to concurrent validity; however, each instrument has barriers that remain before wider adoption can be considered in the setting of pSpA.

A final consideration when selecting, or developing, an instrument for the assessment of disease activity is the need to assess disease impact. Beckers et al discuss the discordance between instruments when classifying patients into the disease activity states.<sup>5</sup> The discordance between patient and physician assessment of disease has been previously reported in a number of immune-mediated inflammatory diseases including PsA.<sup>9</sup> In the study by Beckers et al,<sup>5</sup> some of the discordance is likely to be due to the different components of the PASDAS, DAPSA, and ASDAS instruments. Each of these instruments has slightly different representations of patient and physician components and it is worth considering that impact should be assessed alongside activity, such that symptoms from noninflammatory causes can be addressed accordingly. Disease activity generally refers to reversible pathophysiological manifestations that can be ameliorated with effective pharmacological therapy. Impact of disease includes all the ways in which an individual can be affected by a disease, including irreversible manifestations such as damage and nondisease factors such as self-management.<sup>10</sup> Disease activity and impact may require treatment escalation, but there are advantages in measuring disease activity and impact separately. GRAPPA voted that impact should be assessed separately from activity in PsA using the Psoriatic Arthritis Impact of Disease,<sup>11</sup> and there may be advantages to a similar approach in the wider setting of pSpA.

There is a clear, unmet need, particularly for patients with nonpsoriatic pSpA, where interventional studies are very limited. The study by Beckers et al<sup>5</sup> in this issue of *The Journal* provides information on some of the composite scores that could be utilized to measure treatment effect, alongside other measures previously studied in the ABILITY-2 population. However, the question of the gold standard in arthritis disease activity in

the RCT and routine practice settings remains a complex issue. Future studies would benefit from both patient and physician anchor statements around disease activity and response to help identify the optimal tools for further research.

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