**Article:**
Webers, C., Ortolan, A., Nikiphorou, E. et al. (2026) Peripheral manifestations in spondyloarthritis: a systematic literature review on their assessment and the effect of biological/targeted synthetic DMARDs. Rheumatology, 65 (2). keag042. ISSN: 1462-0324

https://doi.org/10.1093/rheumatology/keag042

*Rheumatology*, 2026, 65(2), keag042
https://doi.org/10.1093/rheumatology/keag042
Published: 28 January 2026
**Systematic Review and Meta Analysis**

British Society for Rheumatology RHEUMATOLOGY OXFORD

# Peripheral manifestations in spondyloarthritis: a systematic literature review on their assessment and the effect of biological/targeted synthetic DMARDs

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## Abstract

***Objectives:*** **Peripheral manifestations (peripheral arthritis/enthesitis/dactylitis) are frequent in axial spondyloarthritis (axSpA) yet, understudied. We (i) evaluated the assessment/reporting of peripheral manifestations in trials of biological or targeted synthetic DMARDs (b/tsDMARDs) for axSpA and peripheral SpA (pSpA), and (ii) synthesized the efficacy of b/tsDMARDs on these manifestations.**

***Methods:*** **Systematic literature review (SLR) of controlled trials evaluating b/tsDMARDs in axSpA/pSpA (excluding psoriatic arthritis). Records were identified through previous SLRs informing ASAS-EULAR recommendations and updated searches. Outcomes included (i) frequency of assessment/reporting of peripheral arthritis/enthesitis/dactylitis and (ii) treatment efficacy of b/tsDMARDs on these peripheral manifestations [standardized mean differences (SMDs) or relative risk].**

***Results:*** **We included 100 axSpA and four pSpA trials. In axSpA, peripheral arthritis was assessed in 54%, enthesitis in 64% and dactylitis in only 10% of studies. When assessed, results were reported in 69%, 72% and 10% of studies, respectively, and often in all patients (instead of those affected at baseline). Most frequently used instruments were 44-joint count for peripheral arthritis (48%), Maastricht Ankylosing Spondylitis Enthesitis Score for enthesitis (88%) and digit count for dactylitis (40%). Composite indices like DAS were not used. SMDs (range 0.26 to −1.18) indicated mainly small-to-moderate b/tsDMARD effects, typically higher in patients with baseline peripheral involvement. In pSpA, peripheral manifestations were always assessed/reported, with generally moderate effects (SMD range −0.10 to −1.22).**

***Conclusion:*** **Peripheral manifestations are inconsistently assessed and reported in axSpA trials. While b/tsDMARDs have small-to-moderate effects on peripheral manifestations, these may be underestimated due to not being assessed in the population affected at baseline.**

**Keywords** spondyloarthritis, peripheral manifestations, peripheral arthritis, enthesitis, dactylitis, measurement, trials

**Received:** 29 September 2025. **Accepted:** 31 December 2025

**Rheumatology key messages**

- Peripheral manifestations, especially peripheral arthritis and dactylitis, are understudied and under-reported in axSpA trials.
- Analyses show small to moderate b/tsDMARD effects, though often including patients without peripheral manifestations.
- In pSpA, b/tsDMARD trials consistently assess and report on peripheral manifestations.

# Introduction

Spondyloarthritis (SpA) is an inflammatory disease characterized by axial and peripheral musculoskeletal involvement. A distinction is made between axial SpA (axSpA), predominantly affecting the spine and sacroiliac joints, and peripheral SpA (pSpA), where peripheral arthritis, enthesitis and dactylitis are the main manifestations [1, 2]. AxSpA in fact represents a spectrum, including severe forms with structural damage to the sacroiliac joints (radiographic axSpA, r-axSpA) but also forms without relevant radiographic changes (non-radiographic axSpA, nr-axSpA) [1].

Despite the classification in axSpA and pSpA, there is substantial overlap between these in clinical practice. Yet, peripheral manifestations (i.e. peripheral arthritis, enthesitis and dactylitis) in axSpA receive less attention, even though they occur in around 30% of patients [3]. Studies in axSpA usually focus on outcomes related to axial manifestations, while peripheral manifestations are considered only as a secondary outcome (at best). However, peripheral manifestations contribute to the disease burden and are associated with worse outcomes [4, 5]. As such, improvement in these outcomes would likely be beneficial for patients. While the effect of important axSpA therapies, such as biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs), on axial symptoms has been well-documented, their impact on peripheral manifestations remains less clear [6, 7].

A comprehensive synthesis on how peripheral manifestations in axSpA populations are assessed in studies, and the effect of b/tsDMARDs on these manifestations, is lacking. Such a synthesis would provide insight into which instruments are actually being used to assess peripheral manifestations in axSpA, and to what extent there is heterogeneity in their assessment. This information could help standardize future research in the field. In addition, if efficacy in b/tsDMARD studies is included in this synthesis, it could demonstrate the potential benefits of these therapies for peripheral manifestations specifically. Finally, evidence from similar studies in pSpA, where these manifestations are the hallmark of disease and thus likely to be included as outcomes, could supplement the findings in axSpA.

Therefore, our objectives were to evaluate (Objective 1) the frequency of assessment and reporting of each peripheral manifestation in clinical trials of b/tsDMARDs in axSpA and pSpA [psoriatic arthritis (PsA) excluded] and (Objective 2) the efficacy of these drugs on each peripheral manifestation.

# Methods

This preregistered systematic literature review (SLR; CRD42024532666 [8]) was conducted for the Spondyloarthritis and Peripheral Arthritis Disease Activity Instrument Selection and Evaluation project of the Assessment of SpondyloArthritis international Society (ASAS-SPARADISE). ASAS-SPARADISE aims to select the most adequate and best-performing instrument to assess disease activity due to peripheral arthritis in SpA.

# Eligibility and literature search

The scope and eligibility criteria for studies were defined using the PICOT framework (Population/Intervention/Comparator/Outcome/Type of study). Eligibility criteria for Objectives 1 and 2 were the same, except for the outcome (assessment/reporting *vs* treatment effects). Eligible populations were adults with a clinical diagnosis of axSpA (r-axSpA/nr-axSpA) or pSpA. Studies on PsA were not eligible, as we considered this as a separate entity with other (composite) endpoints, which are outside the scope of this review. Studies that also included other diagnoses were eligible if the results for SpA were reported separately. Eligible interventions were any type, duration and formulation of b/tsDMARD, including (but not limited to) TNF-$\alpha$ inhibitors (TNFi), interleukin-17 inhibitors (IL-17i), interleukin-23 inhibitors (IL-23i) and Janus kinase inhibitors (JAKi). Comparators could be of any kind, either active treatment or placebo. Outcomes for Objective 1 were the frequency of assessment and reporting of each peripheral manifestation (peripheral arthritis/joint involvement, enthesitis, dactylitis) using instruments specific to these outcomes, and the frequency of use of each instrument. These instruments could be physician-assessed [e.g. swollen/tender joint count (SJC/TJC), enthesitis count, dactylitis count] or patient-reported [e.g. question 3 or 4 of the BASDAI (BASDAI Q3/Q4)]. Finally, combined indices that captured peripheral manifestations but also other outcomes [e.g. BASDAI, Axial Spondyloarthritis Disease Activity Score (ASDAS)] were also assessed. For Objective 2, studies reporting change from baseline or follow-up scores/status (e.g. resolution of peripheral arthritis) were considered. Eligible types of study were randomized clinical trials (RCTs) and controlled clinical trials (CCTs). Only studies with full-length articles were eligible.

For axSpA, previously conducted SLRs on b/tsDMARD efficacy for the 2016/2022 updates of the ASAS-EULAR management recommendations for axSpA served as a starting point [6, 7, 9]. All clinical trials that were included in these SLRs were eligible for Objective 1, and those that reported the effect of treatment on peripheral manifestations were considered for Objective 2. An expert librarian developed the search strategies for these SLRs which covered the period from 1 January 2009 up to 31 December 2021. This librarian then conducted the same search strategy to cover the period from 1 January 2022 to 4 March 2024.

For pSpA, the approach was similar. The search files for the previous axSpA SLRs and the 2022–2024 search update for the current study were used. Importantly, the search strategy for

these searches was not limited to axSpA specifically but would capture any type of SpA (including pSpA). The searches for both axSpA and pSpA were comprehensive, employing all relevant subject headings and text words to represent the population and intervention. Databases searched were: MEDLINE, Embase, The Cochrane Database of Systematic Reviews and CENTRAL. The search strategies are available in Supplementary File S1.

## Study selection, data extraction and risk of bias assessment

For literature up to 2021, all b/tsDMARD trials in axSpA as identified in the previous SLRs were checked and included by two reviewers. Of note, these two reviewers were also the original reviewers for the SLRs informing the 2022 update of the ASAS-EULAR management recommendations for axSpA. For literature on axSpA from 1 January 2022 onward, the same two reviewers carried out the screening, data extraction and risk of bias (RoB) assessment. Each step started with the evaluation of 20% of records by both reviewers: if their agreement was sufficient (kappa $>0.90$), the remaining records were split between them and evaluated individually. Disagreements (in the double-screened subset) and questions were discussed for consensus, and a methodologist acted as adjudicator if necessary. Records not meeting the selection criteria were excluded, and the reason for exclusion was documented. For literature on pSpA, screening and selection were conducted by a single reviewer.

Data were extracted using a predefined data extraction sheet. Extracted data included general study characteristics, demographics, disease characteristics, inclusion/exclusion criteria, intervention characteristics, comparator characteristics and outcome. Importantly, for Objective 1, study protocols and trial registrations were also checked, where available, either via the original publication or from clinicaltrials.gov and similar websites, to verify whether outcomes had been assessed even when not explicitly reported in the selected articles.

RoB was assessed using the Cochrane Collaboration's tool for RCTs [10]. For articles extracted from the previous SLRs (2016 and 2022), the RoB was not re-assessed, but the RoB formerly assigned to each record by the original review team was reported. The newly identified records (axSpA trials from 2022 to 2024, and pSpA trials) were evaluated for the current SLR.

## Data synthesis

For Objective 1, data were summarized using descriptive statistics. For Objective 2, for each outcome, the effect size of the intervention compared with the comparator at the time of the primary end point assessment was calculated. For continuous outcomes, the standardized mean difference (SMD) was calculated as the mean difference between the outcome change from baseline in the intervention arm and the comparator arm, divided by the pooled standard deviation of change, and interpreted as: SMD $<0.5$ small, 0.5–0.8 moderate, $>0.8$ large effect (with negative SMDs indicating effects that favour intervention over control). SMDs allow for comparisons between studies that use different instruments with different ranges. When the change from baseline was not available, the SMD was calculated using the follow-up outcome values instead. As SMDs for change from baseline and SMDs for follow-up status are not necessarily comparable, these were presented separately. Dichotomous outcomes (e.g. complete resolution of each peripheral manifestation) were assessed using relative risk (RR). Clinical and methodological heterogeneity across studies precluded meta-analysis.

# Results

## Study selection

For axSpA, a total of 83 eligible trials were identified in the previous SLRs. The updated search (2022–2024) yielded 5287 records after de-duplication, in which an additional 17 trials on axSpA were identified, resulting in a total of 100 trials for axSpA (Supplementary Fig. S1). For pSpA, four trials were included.

## Study characteristics

Among the 100 axSpA trials, r-axSpA was the most frequent subtype included ($n=66$ studies). Most included studies investigated bDMARDs ($n=92$) (Supplementary Tables S1 and S2). Studies typically compared active treatment to placebo ($n=57$), although some studies involved a head-to-head comparison ($n=23$), usually in the context of a biosimilar *vs* originator comparison. Twelve studies investigated b/tsDMARD tapering or complete withdrawal. Studies were generally of low RoB ($n=55$) or showed some concerns ($n=26$). Among the four pSpA trials, three investigated TNFi and one a tsDMARD, all compared with placebo [11–14]. Two of them were judged as having low RoB, and two as showing some concerns (Table 1). Of note, the eligibility criteria in the pSpA trials were quite heterogeneous, and presence of psoriasis or axial involvement was not excluded in all trials (e.g. CRESPA and Paramarta 2016 trials [12, 14]).

## Frequency of assessment and reporting of peripheral manifestations (objective 1)

All axSpA studies used composite indices that captured peripheral manifestations, such as ASDAS or BASDAI, but only in one case (1 [1%]; ASTERA [15]) they also described the composite indices in the subpopulation with peripheral manifestations at baseline. When only considering instruments specific for peripheral manifestations, peripheral arthritis was assessed in only half of the studies ($n=54$ [54%]). Among these, 37 studies (69%) reported results, but only 11 (20%) did so in the specific subpopulation with arthritis at baseline. Enthesitis assessment was slightly more frequent, with 64 (64%) studies collecting specific enthesitis outcomes, of which 46 (72%) also reported results, and 16 (25%) in the subpopulation with enthesitis at baseline. Dactylitis was only collected in 10 studies, and results were reported in one study (Fig. 1). There was a tendency towards a higher probability of assessment of peripheral manifestations in lower RoB categories (low or some concerns) (Supplementary Fig. S2). Of note, none of the studies at high RoB reported results in the subpopulation with peripheral manifestations at baseline.

**Table 1** Assessment of peripheral manifestations in trials of bDMARDs and tsDMARDs in pSpA.

| Study | Population[b] | Intervention | N | Time (wks) | Primary end point | Assessment/reporting of peripheral manifestations[a] | | | RoB |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Peripheral arthritis | Enthesitis | Dactylitis | |
| ABILITY-2 (2015) [11] | ASAS+ No PsO/PsA/AS | Adalimumab 40 mg | 165 | 12 | PSpARC40[c] | SJC76<br>TJC78 | Total enthesitis count<br>LEI<br>MASES<br>SPARCC<br>Enthesitis index | Count | Low |
| CRESPA (2017) [12] | ASAS+ Early disease | Golimumab 50 mg | 60 | 24 | Clinical remission[d] | SJC76<br>TJC78<br>BASDAI Q3 | MASES (modified)<br>BASDAI Q4 | Count | Low |
| TIPES (2013) [13] | ESSG/Amor+ No PsA/AS | Adalimumab 40 mg | 40 | 12 | Patient global | SJC66<br>TJC68 | Not assessed | Not assessed | Some concerns |
| Paramarta *et al.* (2016) [14] | ESSG+ Arthritis[e] | Nilotinib 400 mg | 13 | 12 | Patient global & physician global | SJC66<br>TJC78 | Not assessed | Not assessed | Some concerns |

All pSpA trials used placebo as comparator.

[a] For all instruments shown here, results were also reported in the respective studies.

[b] ASAS: ASAS classification criteria for pSpA.

[c] Defined as ≥40% improvement (≥20 mm absolute improvement) from baseline in PtGA of disease activity and PtGA of pain, and ≥40% improvement in at least one of the following: (i) SJC76 + TJC78, (ii) total enthesitis count or (iii) dactylitis count.

[d] Defined as absence of peripheral arthritis, enthesitis and dactylitis.

[e] Study enrolled both pSpA and axSpA patients: patients that fulfilled the ESSG criteria and had arthritis were enrolled as 'pSpA' patients, those with IBP were enrolled as 'axSpA' patients.

AS: ankylosing spondylitis; ASAS: Assessment in SpondyloArthritis international Society; BASDAI Q3/Q4: Bath Ankylosing Spondylitis Disease Activity Index Question 3/Question 4; bDMARD: biological disease-modifying antirheumatic drug; ESSG: European Spondylarthropathy Study Group; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; PsA: psoriatic arthritis; PsO: psoriasis; pSpA: peripheral spondyloarthritis; PSpARC: Peripheral SpA Response Criteria; RoB: risk of bias; SJC: swollen joint count; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC: tender joint count; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

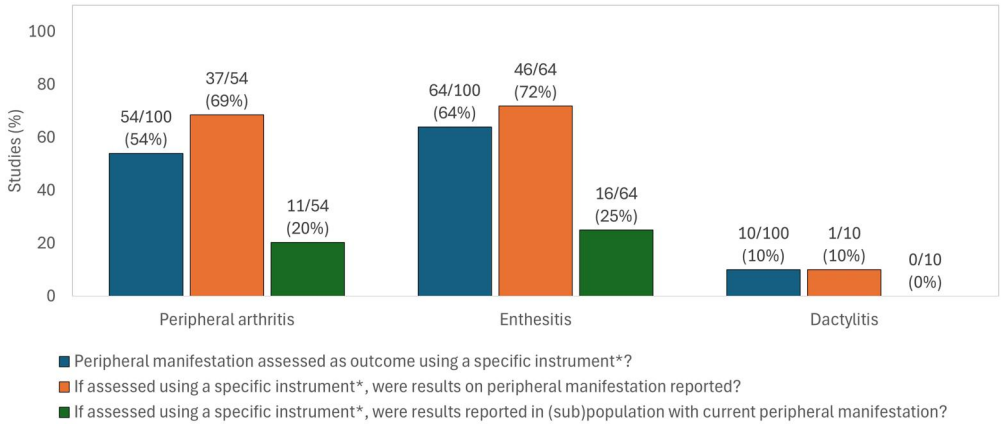


**Figure 1** Assessment and reporting of peripheral manifestations in bDMARD and tsDMARD trials in axSpA. Number (percentage) of studies that assessed each peripheral manifestation as outcome and reported the results on this outcome in general, and in the population with current peripheral manifestation (i.e. those with active peripheral manifestation at baseline). *Specific instrument = instrument specific for assessment of peripheral manifestations (such as a swollen joint count for peripheral arthritis). axSpA: axial spondyloarthritis; bDMARD: biological disease-modifying antirheumatic drug; tsDMARD: targeted synthetic disease-modifying antirheumatic drug

There was no clear trend over time in assessment or reporting of peripheral manifestations (Supplementary Fig. S3).

In pSpA, all four studies (100%) assessed and reported on peripheral arthritis, and two trials (50%) assessed enthesitis and dactylitis (Table 1). This was in the population with peripheral manifestations at baseline, as these studies required patients to have active peripheral manifestations to be enrolled. Almost all patients had active peripheral arthritis at baseline (prevalence range 93–100%), while enthesitis and dactylitis prevalence at baseline varied and was not always reported.

When considering which specific instruments were used, in axSpA, the most frequently used instruments for peripheral arthritis (assessed in 54 studies) were SJCs based on 44 joints (48%), 66 joints (13%) and 64 joints (9%), and TJCs based on 44 joints (22%), 46 joints (15%) and 68 joints (13%) (Supplementary Fig. S4). No studies used composite scores involving joint counts, such as the Disease Activity in Psoriatic Arthritis (DAPSA). For enthesitis (assessed in 64 studies), the majority of studies used the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES, 88%), followed by the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index (11%), BASDAI Q4 (8%) and the Leeds Enthesitis Index (LEI, 3%) (Supplementary Fig. S5). Several studies used multiple instruments to assess enthesitis. The main instrument used for dactylitis was digit count (40%), while in three studies it was collected as an adverse event. The four included pSpA trials all used swollen (SJC66/SJC76) and tender (TJC68/TJC78) joint counts to assess peripheral arthritis. Enthesitis and dactylitis were assessed in two of these trials, using multiple instruments per study for enthesitis (total enthesitis count, LEI, SPARCC enthesitis index, MASES and BASDAI Q4) and a digit count for dactylitis.

Imaging outcomes related to peripheral manifestations were also captured. One axSpA study and one pSpA study assessed peripheral arthritis and enthesitis using (whole-body) MRI [16–19]. In addition, one study in patients with axSpA or PsA assessed heel enthesitis using MRI, but results were not reported for the axSpA subgroup (non-imaging outcomes on peripheral manifestations were reported for the axSpA subgroup) [20]. One study, with a very small study population and a high RoB, investigating a local bDMARD injection, reported ultrasound results on Achilles enthesitis [21].

## Efficacy of bDMARDs and tsDMARDs on peripheral manifestations (objective 2)

Among the included axSpA trials, 50 (50%) reported efficacy results on any peripheral manifestation. Of these 50 studies, 37 (74%) reported treatment effect on peripheral arthritis, 46 (92%) on enthesitis and only one (2%) on dactylitis. SMDs for change from baseline in peripheral arthritis could be calculated for 16 studies (15 analyses, COAST-V/W were pooled [22]), indicating mainly small effects on peripheral arthritis for both bDMARDs and tsDMARDs, with most SMDs ranging from −0.3 to 0.0 when the whole population (with/without peripheral arthritis) was considered (Fig. 2, Supplementary Table S3). Some studies involved a situation where no difference in effect was expected (i.e. tapering study or comparison of originator *vs* biosimilar). Importantly, only a minority of studies ($n = 3$) reported results in the subgroup with peripheral arthritis at baseline, showing slightly higher effects (SMD ranging up to −0.6). Complete resolution of peripheral arthritis in those affected at baseline ($n = 2$ studies, both investigating bimekizumab [23]) was 58–64% for bimekizumab and 36–42% for placebo (RRs ranging 1.4–1.8 for swollen joint resolution, 1.3–1.7 for tender joint resolution). For enthesitis, results were reported in 46 studies, frequently using the MASES (37 [80%]). SMDs for change from baseline could be calculated for 19 studies (18 analyses, COAST-V/W were pooled [22]) for various instruments, seven of which reported results in the subgroup with enthesitis at baseline. Similar to peripheral arthritis, these SMDs indicated mainly small to moderate effects on enthesitis for both bDMARDs and tsDMARDs (Fig. 3, Supplementary Table S4). One study reported the proportion of patients with ≥20% improvement in MASES (RR 0.9 for apremilast *vs* placebo) [24]. Complete resolution of enthesitis ($n = 5$ studies) occurred in 34–52% of patients for various bDMARDs and 14–33% for placebo (RRs ranging 1.0–3.1 for various enthesitis instruments). SMDs for follow-up outcome values—calculated only when insufficient data on change from baseline were reported—indicated mainly small to negligible effects, although the number of

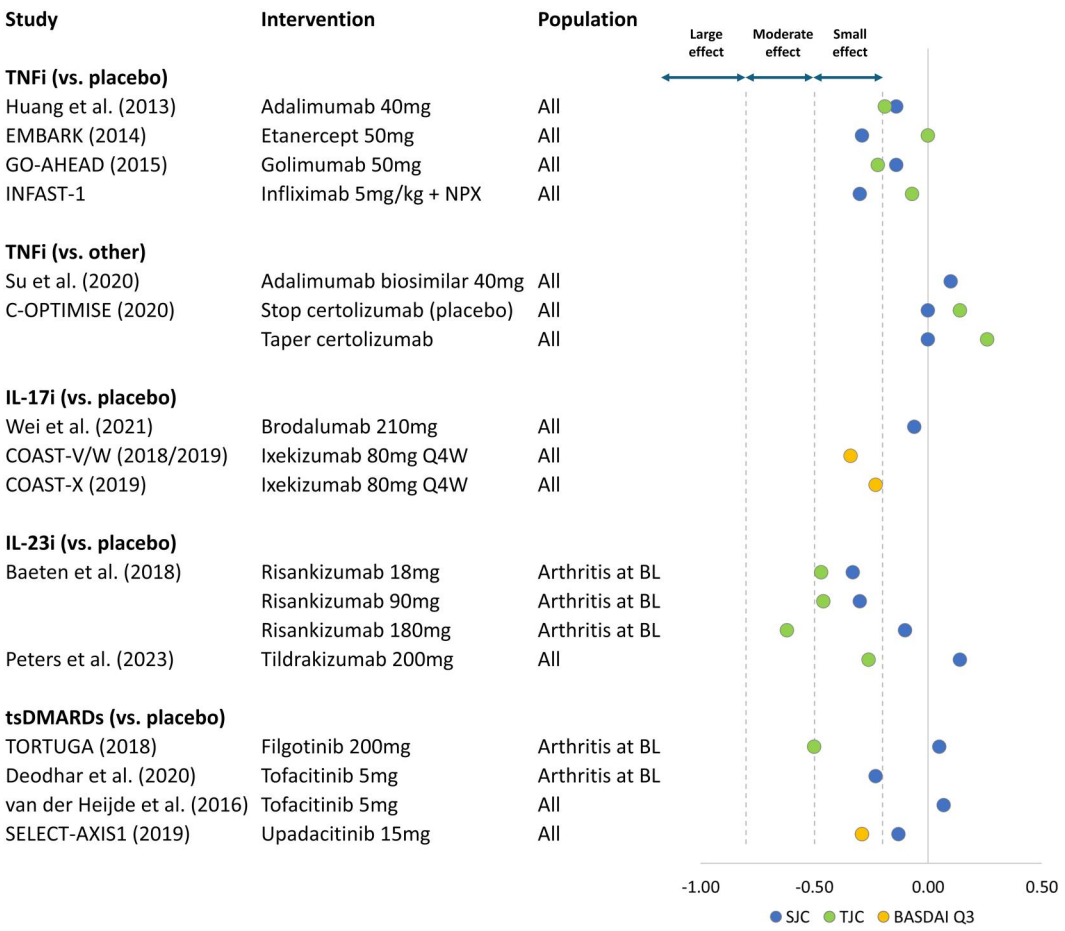


**Figure 2** Efficacy of bDMARDs and tsDMARDs on peripheral arthritis in axSpA trials. The x-axis shows the standardised mean difference (SMD) of the change from baseline in the respective peripheral arthritis instrument for intervention versus comparator (each color indicates a different instrument as specified in the legend). A negative SMD favors the intervention over the comparator. Only studies for which the SMD for change from baseline could be calculated are shown. axSpA: axial spondyloarthritis; bDMARD: biological disease-modifying antirheumatic drug; BL: baseline; IL-17i: interleukin-17 inhibitor; IL-23i: interleukin-23 inhibitor; TNFi: tumor necrosis factor inhibitor; tsDMARD: targeted synthetic disease-modifying antirheumatic drug

studies was limited ($n = 4$ for peripheral arthritis and enthesitis each, respectively) and these often had an active comparator (Supplementary Tables S3 and S4). Finally, for dactylitis, the only study with results available was a TNFi tapering study [25]. Dactylitis counts were similar in both study arms (median of 0 in both), and most patients did not have active dactylitis at baseline as expected in a tapering study.

In pSpA, effect sizes for peripheral arthritis were heterogeneous, ranging from small to large (SMD range −0.10 to −1.22). For enthesitis, a similar heterogeneity was observed, for both instrument type and results, with effects ranging from small to large (SMD range −0.33 to −0.90). SMDs for dactylitis were small (Table 2).

# Discussion

This SLR of b/tsDMARDs trials in SpA demonstrates that peripheral manifestations were assessed in fewer than two-thirds of studies in axSpA, and treatment effects on them were reported in less than half. Especially, peripheral arthritis and dactylitis were understudied and under-reported. We also observed considerable heterogeneity in the instruments used to assess these peripheral manifestations. Even when these outcomes were reported, these were infrequently evaluated in the subpopulation of interest (i.e. those presenting with the specific peripheral manifestation at baseline) [29]. Reported effect sizes were typically small to moderate, particularly when analyses were conducted in the overall axSpA population. In pSpA, peripheral manifestations were assessed and reported in all trials, in the population of interest, and generally with larger effect sizes.

While axial manifestations are expectedly predominant in axSpA, the distinction between axSpA and pSpA is not absolute. Among patients with an axSpA diagnosis, the proportion of patients with both axial and peripheral manifestations is similar to that of purely axial disease [30]. Moreover, peripheral manifestations are associated with a worse prognosis, despite a more intensive drug therapy, contributing to the burden of disease [4, 5, 31]. These observations should prompt a more systematic assessment of peripheral manifestations in axSpA. However, it is not only a matter of suboptimal assessment, but also of incomplete reporting. This observation is surprising, as the first ASAS-OMERACT Core Outcome Set (COS) for axSpA—

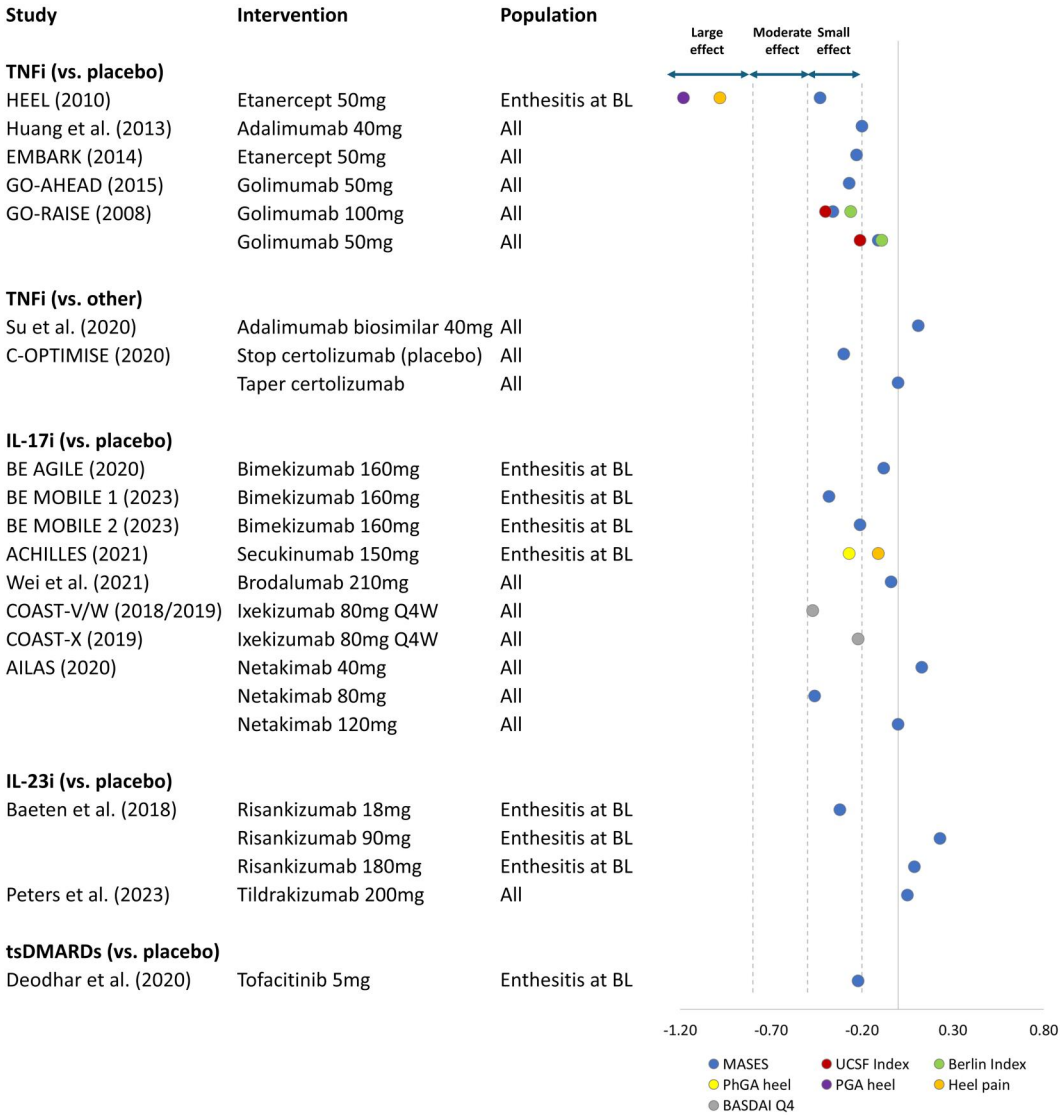


**Figure 3** Efficacy of bDMARDs and tsDMARDs on enthesitis in axSpA trials. The x-axis shows the standardized mean difference of the change from baseline in the respective enthesitis instrument for intervention versus comparator (each colour indicates a different instrument as specified in the legend). A negative SMD favors the intervention over the comparator. Only studies for which the SMD for change from baseline could be calculated are shown. axSpA: axial spondyloarthritis; bDMARD: biological disease-modifying antirheumatic drug; BL: baseline; IL-17i: interleukin-17 inhibitor; IL-23i: interleukin-23 inhibitor; TNFi: tumor necrosis factor inhibitor; tsDMARD: targeted synthetic disease-modifying antirheumatic drug

published over 25 years ago—already included peripheral arthritis and enthesitis as mandatory domains for DMARD trials [32, 33], and a recent update of the COS confirmed the relevance of these manifestations as trial outcomes in axSpA [34, 35]. Somewhat alarmingly, despite the increasing attention to peripheral aspects of axSpA over the last decades, we did not observe an improvement in the assessment or reporting of peripheral manifestations over time in axSpA trials.

Among the different peripheral manifestations, enthesitis was most frequently assessed and reported in axSpA, perhaps due to the availability of instruments specifically developed for this manifestation in axSpA [36, 37]. The MASES was the most frequently used and is also the instrument endorsed as a mandatory measure in DMARD trials in the ASAS COS [35]. For peripheral arthritis, the instrument endorsed by the ASAS COS (SJC44) was most frequently used, but still in less than half of the trials that assessed peripheral arthritis [35]. Dactylitis is much less frequent in axSpA and was rarely assessed [38]. However, it is associated with worse outcomes independently of peripheral arthritis, therefore deserving (more) attention [39]. This is supported by its inclusion in the ASAS COS [34, 35].

In the majority of studies, evaluation of treatment effects was carried out in the whole trial population, which typically includes patients with and without active peripheral manifestations at baseline. This obviously dilutes any effects on peripheral manifestations, as patients cannot show improvement with treatment if they were already unaffected at baseline. The recently issued ASAS recommendations on outcome reporting in trials advise to analyse and report peripheral manifestations in patients with active manifestations at baseline [29]. Furthermore, data on peripheral manifestations can be highly skewed in axSpA, and little is known about thresholds of meaning, making interpretation of results very

**Table 2** Efficacy of bDMARDs and tsDMARDs on peripheral manifestations in pSpA trials.

| Peripheral manifestation | Study | Intervention (I) | Comparator (C) | N (I) | N (C) | Time (weeks) | Instrument | Mean (SD) change, intervention | Mean (SD) change, control | SMD for change (95% CI)[a] | RoB |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Peripheral arthritis | ABILITY-2 (2015) | Adalimumab 40 mg | Placebo | 84 | 81 | 12 | SJC76 | −3.6 (4.3) | −3.1 (5.6) | −0.10 (−0.41–0.21) | Low |
| | | | | | | | TJC78 | −5.9 (8.7) | −1.8 (8.4) | −0.48 (−0.79 to −0.17) | |
| | TIPES (2012) | Adalimumab 40 mg | Placebo | 19 | 19 | 12 | SJC66 | −2.5 (4.0) | −0.4 (1.8) | −0.68 (−1.32 to −0.01) | Some concerns |
| | | | | | | | TJC68 | −1.8 (9.2) | 1.7 (6.5) | −0.44 (−1.07–0.21) | |
| Enthesitis | ABILITY-2 (2015) | Adalimumab 40 mg | Placebo | 84 | 81 | 12 | LEI | −1.4 (1.4)[b] | −0.45 (1.4)[b] | −0.67 (−1.06 to −0.27) | Low |
| | | | | | | | SPARCC Index | −2.4 (3.0)[b] | −1.0 (3.0)[b] | −0.46 (−0.81 to −0.11) | |
| | | | | | | | Total enthesitis count | −3.4 (5.0)[b] | −1.8 (5.0)[b] | −0.33 (−0.66–0.00) | |
| Dactylitis | ABILITY-2 (2015) | Adalimumab 40 mg | Placebo | 84 | 81 | 12 | Count | −1.6 (1.3)[b] | −1.3 (1.3)[b] | −0.24 (−0.91–0.45) | Low |
| **Peripheral manifestation** | **Study** | **Intervention[b]** | **Comparator** | **N** | | **Time (weeks)** | **Instrument** | **Mean (SD) FU score, intervention** | **Mean (SD) FU score, control** | **SMD for FU score (95% CI)** | **RoB** |
| Peripheral arthritis | CRESPA (2017) | Golimumab 50 mg | Placebo | 40 | 20 | 24 | SJC76 | 0.3 (0.8)[c] | 2.3 (4.8)[c] | −0.71 (−1.25 to −0.15) | Low |
| | | | | | | | TJC78 | 0.7 (1.5)[c] | 4.3 (4.8)[c] | −1.22 (−1.78 to −0.62) | |
| | | | | | | | BASDAI Q3 | 1.1 (2.1)[c] | 3.3 (3.8)[c] | −0.78 (−1.32 to −0.22) | |
| Enthesitis | CRESPA (2017) | Golimumab 50 mg | Placebo | 40 | 20 | 24 | Modified MASES | 0.2 (1.0)[d] | 1.3 (2.3)[d] | −0.68 (−1.23 to −0.13) | Low |
| | | | | | | | BASDAI Q4 | 1.0 (1.5)[c] | 3.0 (3.2)[c] | −0.90 (−1.45 to −0.33) | |
| Dactylitis | CRESPA (2017) | Golimumab 50 mg | Placebo | 40 | 20 | 24 | Count | 0.6 (0.4)[d] | 1.0 (1.8)[d] | −0.36 (−0.90–0.18) | Low |

[a] Confidence interval calculated using the method described by Hedges *et al.* [28].
[b] Results reported in figure, extracted using image analysis software. SD not reported but calculated based on *P*-value, using the method from the Cochrane handbook [27].
[c] Reported as median (IQR) change, converted to mean (SD) using the method of Wan *et al.* [26].
[d] Median and 95% confidence interval reported, converted to mean (SD) by imputation of mean with median, and conversion of 95% confidence to SD using the method from the Cochrane handbook.

BASDAI Q3/Q4: Bath Ankylosing Spondylitis Disease Activity Index Question 3/Question 4; bDMARD: biological disease-modifying antirheumatic drug; C: comparator; FU: follow-up; I: intervention; LEI: Leeds Enthesitis Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; pSpA: peripheral spondyloarthritis; RoB: risk of bias; SJC: swollen joint count; SMD: standardized mean difference; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC: tender joint count; tsDMARD: targeted synthetic disease-modifying antirheumatic drug.

difficult [35]. Reliability of both clinical and imaging assessments also varies (e.g. of enthesitis [40]). The included population and the intrinsic limitations of the instruments probably explain why effects observed in this review varied substantially and were generally small to moderate. Also, we considered outcomes at the time of primary end point assessment—often around 16 weeks after treatment initiation—while for enthesitis, improvement can occur at a later time [41].

In pSpA, the number of trials was scarce. However, we observed that effect sizes for b/tsDMARDs on peripheral manifestations generally tended to be slightly higher, albeit with significant heterogeneity. This may in part be explained by the heterogeneity in defining pSpA in these studies. We excluded PsA in our review, as we considered this a separate entity and thus beyond the scope of this review. There has been much debate about the overlap between pSpA and PsA in peripheral manifestations, as well as between axSpA with psoriasis and PsA with axial involvement [3, 42, 43]. However, as PsA typically involves different (composite) endpoints, as well as an additional focus on skin disease, we felt that the results of PsA trials would have limited value for our purpose (i.e. assessment of peripheral manifestations in axSpA). Interestingly, studies focusing on pSpA were not necessarily more recent than those describing axSpA with peripheral manifestations [11–14]. This suggests the unmet need of under-reporting in axSpA is still actual, though this aspect might improve in the next years, with the ASAS COS [35].

Notably, none of the trials considered composite outcomes that include joint counts, such as the DAPSA or DAS, which have been highlighted to have the highest discriminatory capacity to distinguish between active and inactive peripheral disease in a recent ASAS-perSpA analysis [44]. On the one hand, it is understandable that these instruments were not included in axSpA trials because they were not specifically developed for use in this disease. Furthermore, the use of DAS in SpA—particularly its 28-joint count form—is strongly criticized because it omits joints that are frequently involved in this disease [45]. On the other hand, validity and discriminative capacity of some composite indices including DAPSA has been demonstrated to be acceptable, and independent of concomitant psoriasis, in pSpA [46]. This suggests that composite indices could be useful for evaluation of disease activity (including disease activity due to peripheral arthritis) in axSpA [44].

Strengths of our methodology include the broad search strategy that captured both axSpA and pSpA, as well as all outcomes assessing peripheral manifestations. Also, the thorough assessment of not only actual reports but also study protocols and trial registrations contributed to the validity of our findings.

Several limitations deserve discussion. First, heterogeneity between the included studies precluded meta-analysis. Second, despite our efforts to correctly identify assessment and reporting on peripheral manifestations, it is still possible that we misclassified some studies (false negatives). For example, we discovered that peripheral manifestations were collected in ABILITY-1 only after a specific data request for (unrelated) investigator-initiated research [47]. For this review, it was not feasible to contact all data owners for confirmation. However, the fact that peripheral manifestations were never mentioned as outcome is still significant and might be considered as a limitation pertaining to the original studies, rather than to this SLR. Third and finally, for the identification of studies published before 2022, we relied on search files from previous SLRs [6, 7, 9]. However, those SLRs were conducted rigorously, and several of the involved researchers were part of the current review team.

In conclusion, peripheral arthritis, enthesitis and dactylitis are often under-reported in b/tsDMARD trials in axSpA. In pSpA, their assessment is, by definition, more structured; however, the overall body of evidence remains considerably limited. The modest effect sizes of these drugs typically observed for peripheral domains may be partly explained by the intrinsic limitations of the instruments employed, as well as by the selection criteria for trial populations and analysis. As these manifestations contribute to the burden of disease, there is a clear unmet need for patients that can only be solved through a more systematic and standardized evaluation of peripheral manifestations, as well as the effect of treatment on them. This will not only improve patient outcomes but also enhance our understanding of drug efficacy across the full spectrum of SpA manifestations.

## Supplementary material

Supplementary material is available at *Rheumatology* online.

## Data availability

The full data extraction files are available from the corresponding author upon reasonable request.

## Contribution statement

Casper Webers (Formal Analysis, Investigation, Data Curation, Visualization, Writing—Original Draft), Augusta Ortolan (Formal Analysis, Investigation, Data Curation, Visualization, Writing—Original Draft), Elena Nikiphorou (Formal Analysis, Investigation, Writing—Review & Editing), Alexandre Sepriano (Formal Analysis, Investigation, Writing—Review & Editing), Louise Falzon (Investigation, Writing—Review & Editing), Clementina López-Medina (Formal Analysis, Investigation, Writing—Review & Editing), Dafne Capelusnik (Formal Analysis, Investigation, Writing—Review & Editing), Désirée van der Heijde (Formal Analysis, Investigation, Writing—Review & Editing), Anna Moltó (Conceptualization, Formal Analysis, Investigation, Visualization, Writing—Review & Editing, Supervision, Project Administration, Funding Acquisition), Sofia Ramiro (Conceptualization, Formal Analysis, Investigation, Visualization, Writing—Review & Editing, Supervision, Project Administration, Funding Acquisition).

## Funding

This work was funded by the Assessment of SpondyloArthritis international Society (ASAS) as part of the ASAS-SPARADISE project.

*Disclosure statement:* C.W. reports honoraria from Novartis. A.O. reports speaker or travel fees from Abbvie, Astra Zeneca, Eli Lilly, Johnson & Johnson, GSK, Novartis and UCB. E.N. reports speaker honoraria and/or participated in advisory boards for

UCB, Pfizer, Gilead, Galapagos, AbbVie, Eli Lilly, Alfasigma, Fresenius, Novartis and research grants from Pfizer and Eli Lilly. E.N. also holds the role of Associate Editor for *Rheumatology* and has not peer reviewed or made any editorial decisions on this article. A.S. reports speaking and/or consulting fees from AbbVie, Novartis, UCB and Lilly, and support for attending conferences from Janssen and Lilly. C.L.-M. reports consulting fees from Johnson & Johnson, UCB, Novartis, Eli Lilly and Abbvie; grants from UCB, Eli Lilly, Abbvie and UCB; and speaking fees from Johnson & Johnson, UCB, Novartis, Eli Lilly and Abbvie. D. v.d.H. reports consulting fees from AbbVie, Alfasigma, ArgenX, BMS, Eli-Lilly, Grey-Wolf Therapeutics, Janssen, Novartis, Pfizer, Takeda and UCB Pharma; is an Associate Editor for *Annals of the Rheumatic Diseases* and Editorial board member for *Journal of Rheumatology*; and is Director of Imaging Rheumatology BV. A. M. reports bursaries, honoraria and travel reimbursement from Abbvie, Alphasigma, Biogen, BMS, Janssen, Lilly, Novartis, Pfizer and UCB. S.R. reports consultancy/advisory fees from AbbVie, Alfasigma, Eli Lilly, Johnson & Johnson, MSD, Novartis, Pfizer and UCB; funding/grants from AbbVie, Alfasigma, Eli Lilly, MSD, Novartis, Pfizer and UCB; speaking/lecture fees from AbbVie, Alfasigma, Eli Lilly, Johnson & Johnson, MSD, Novartis, Pfizer and UCB; travel reimbursement from AbbVie, Eli Lilly and UCB; and is a member of the ASAS Executive Committee. L.F. and D.C. declare no potential conflicts of interest.

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Rheumatology, 2026, 65, 1–11
https://doi.org/10.1093/rheumatology/keag042
Systematic Review and Meta Analysis