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Anna Molto, Joachim Sieper

► **To cite this version:**

Anna Molto, Joachim Sieper. Peripheral spondyloarthritis: Concept, diagnosis and treatment. *Best Practice and Research: Clinical Rheumatology*, 2018, 32, pp.357 - 368. 10.1016/j.berh.2019.02.010 . hal-03484739

**HAL Id: hal-03484739**

**<https://hal.science/hal-03484739v1>**

Submitted on 20 Dec 2021

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## Peripheral spondyloarthritis : concept, diagnosis and treatment

Authors : Anna MOLTO<sup>1,2</sup> and Joachim SIEPER<sup>3</sup>

1: Rheumatology Department, Cochin Hospital, Assistance Publique Hôpitaux de Paris, Paris, France

2: INSERM (U-1153), CRESS, Paris, FRANCE

3: Rheumatology, Charité, Campus Benjamin Franklin, 12200 Berlin, Germany

Corresponding author: Anna MOLTO

Rheumatology Department, Cochin Hospital

27 rue du Faubourg Saint Jacques

75014, Paris, FRANCE

[anna.molto@aphp.fr](mailto:anna.molto@aphp.fr)

**Key words:** Peripheral Spondyloarthritis; arthritis; enthesitis; dactylitis

Conflict of interest:

- Anna MOLTO: Honorary for consultancy: Abbvie, Janssen, Lilly, Novartis, UCB, Pfizer,
- Joachim SIEPER: Honorary for consultancy or member of speaker's bureau: Abbvie, Boehringer-Ingelheim, Janssen, Lilly, Novartis, UCB, Pfizer, Merrck, Mylan
- 

**Funding:** Anna MOLTO has received grants from Pfizer and UCB

**Practice points:**

- Diagnosis of peripheral Spondyloarthritis can be challenging, in particularly in the absence of extra-articular manifestations such as uveitis, psoriasis or inflammatory bowel disease.
- Evaluation of disease activity should always include assessment of objective signs of inflammation, particularly in the presence of enthesitis as the sole peripheral manifestation, mainly due to the potential overlap with fibromyalgia tender points.
- NSAIDs and glucocorticoids are recommended as the first step of treatment in all peripheral manifestations, while conventional synthetic DMARDs seem only efficacious in arthritis.

**A research agenda**

- The prevalence of Peripheral Spondyloarthritis, even within the whole group of spondyloarthritis, has not been well studied yet.
- Several biologics and targeted synthetic DMARDs (TNFi, antiIL17, JAK-inhibitors) have been proven to be efficacious in peripheral involvement in PsA (arthritis and enthesitis), but studies on peripheral SpA are lacking.

**Abstract:**

Peripheral spondyloarthritis refers to spondyloarthritis with predominant peripheral (arthritis, enthesitis or dactylitis) involvement. Diagnosis can be challenging, particularly in the absence of SpA extra-articular manifestations such as uveitis, psoriasis or inflammatory bowel disease. Evaluation of disease activity should always include assessment of objective signs of inflammation, particularly in the presence of enthesitis as the sole peripheral manifestation, mainly due to the potential misdiagnosis with fibromyalgia tender points. Several recommendations for management/treatment of psoriatic arthritis have been published by EULAR and GRAPPA, but none for peripheral SpA in general. NSAIDs and glucocorticoids are recommended as the first step of treatment in all peripheral manifestations, while conventional synthetic (cs) DMARDs seem only efficacious in arthritis. Several biologics and targeted synthetic (ts) DMARDs (TNFi, antiIL17, JAK-inhibitors) have been proven to be efficacious in peripheral involvement in PsA (arthritis and enthesitis), but studies on peripheral SpA are lacking.

## 1. The concept of peripheral spondyloarthritis

The word spondyloarthritis (SpA) derives from the greek *spondylo-* (vertebrae) *arthr-* (joint) and *-itis* (inflammation). This multifaceted systemic disease [1], encompasses inflammation of the axial skeleton (axial SpA, axSpA), and extra-articular symptoms, such as psoriasis, uveitis, or inflammatory bowel disease, but also articular extra-axial manifestations, i.e. enthesitic and peripheral articular involvement.

Moll and colleagues[2] were, in 1974, the first authors to coin the spondyloarthritis “concept”, highlighting a number of signs and symptoms that clustered entities that were at that time considered separated diseases, including entities with predominantly peripheral manifestations, such as psoriatic arthritis (PsA), arthritis related to inflammatory bowel disease (IBD), or reactive arthritis. Indeed, the shared characteristics of these entities with axSpA or its prototype, radiographic axSpA (also known as ankylosing spondylitis) can appear in the same individual (simultaneously or at different time-points over the course of the disease) and also in a family member (e.g. a patient can be diagnosed both from psoriasis and his father from Crohn’s disease). [3] The same group of authors suggested later that all these diseases shared a common genetic background, by confirming the significantly higher prevalence of Human Leukocyte Antigen (HLA)-B27 in patients suffering from these diseases.[4–6] (Table 1) . However, a substantial proportion of patients with peripheral SpA presents with a similar clinical picture and genetic background but without the presence of specific accompanying diseases such as psoriasis, IBD or a preceding infection.[7,8] The prevalence of peripheral SpA as a whole has not been (yet) properly evaluated; a systematic literature review [9] estimated the prevalence of psoriatic arthritis and SpA related to inflammatory bowel disease (IBD) to be of 0.25% and 0.08% [10–12], respectively.

Based on these shared conditions, the term ‘peripheral spondyloarthritis’ applies to patients fulfilling the diagnosis of spondyloarthritis, but with predominant involvement of peripheral joints, entheses and tendons, rather than the involvement of spine and axial skeleton.[13]

However, the entities described under peripheral SpA may differ in terms of prognosis, outcomes, and even response to therapies. For example, reactive arthritis (ReA) has a high spontaneous remission rate that is not seen in PsA[14] and post-Chlamydia ReA may respond to long- term antibiotics while other peripheral SpA conditions will not. [15] Most conditions

under peripheral SpA have association with HLA- B27, but the proportion varies widely between 50-70% in white Caucasian patients with ReA to no association seen in peripheral enteropathic arthritis.[4] The functional, imaging, and outcome measures validated in PsA patients have not been tested in other peripheral SpA conditions, and we do not know if they will work as well in non- psoriatic peripheral SpA. The typical clinical presentations of articular involvement in peripheral SpA is an asymmetric, mono- , or oligoarticular (less than five joints) inflammatory arthritis that involves the lower limbs more frequently than the upper limbs and is characteristic for all sub-types of peripheral arthritis including PsA. Whether a symmetric or asymmetric polyarticular (more than 4 joints) inflammatory arthritis involving often the distal-interphalangeal joints, [16] another (and probably more frequent) subtype of clinical presentation in PsA, should also be seen as part of peripheral SpA is still under debate. However, based on the observed data,[17,18] a huge overlap of clinical rheumatological manifestations exists among PsA and all other forms of peripheral SpA (axial symptoms, peripheral enthesitis, dactylitis) with PsA probably being the most frequent SpA subtype. [19]. However, undifferentiated peripheral SpA (i.e. peripheral SpA presenting without known psoriasis, IBD or preceding infection) was the most frequent peripheral SpA subtype, according to the diagnosis of the local rheumatologist, when patients presented with a clinical picture compatible with peripheral SpA but without diagnosis, as part of the 'Assesment in Spondylo-Arthritis international Society' (ASAS) classification criteria study.[20] But PsA was probably underrepresented in this study because a diagnosis of PsA might be easier to be made for the non-specialist and therefore these patients might less frequently be referred.

**Table 1: Prevalence of HLAB27 in Ankylosing Spondylitis and related diseases**

	N° in group	% with HLAB27	Reference
Controls		7-10	
Ankylosing Spondylitis	75	96	Brewerton and others (1973)
	40	83	Schlosstein and others (1973)
Reactive arthritis			
• Peripheral	23	65	Brewerton and others (1973)
• Spinal	10	100	
• Peripheral	19	95	Morris and others (1974)
• Spinal	6	100	
• Peripheral	19	53	McClusky and others (1974)
• Spinal	11	82	
Inflammatory bowel disease			
• Peripheral	8	12.5	Brewerton and others (1974)
• Spinal	20	65	
• Peripheral	14	0	Bluestone and others (1974)
• Spinal	12	67	

Adapted from Lambert JR, et al. Ann Rheum Dis. 1976. [4]

## 2. The diagnosis of peripheral spondyloarthritis

No validated diagnostic criteria are available for peripheral SpA, and diagnosis is based on the presence of several signs and symptoms as discussed above. A diagnostic algorithm for reactive arthritis based on rheumatic manifestations typical for peripheral SpA plus clinical and laboratory evidence of a preceding infection of the gastrointestinal or urogenital tract has been proposed [21], but not for the other peripheral SpA subtypes. However, in patients with psoriasis [22] or IBD with typical peripheral SpA manifestations a diagnosis of peripheral SpA is likely, although other explanations for the rheumatic symptoms have always to be considered and excluded. The diagnosis is more difficult for the 'undifferentiated' peripheral SpA: a positive HLA-B27 testing is helpful here and/or the presence of several other clinical parameters suggestive of SpA (see Fig 1).

In some patients, there may be a preceding infection with specific bacteria (i.e. Salmonella, Shigella, Yersinia, Campylobacter, and Chlamydia). These patients may also develop axial symptoms, inflammatory back pain and even subsequent sacroiliitis, and depending on the predominant manifestations (i.e. peripheral or axial) they would be considered to have peripheral SpA or axSpA.

As for the whole group of SpA, uveitis anterior at present or in the past can occur in peripheral SpA, especially in HLA-B27 positive patients.

Clinical examination should always confirm the inflammatory nature of peripheral involvement, whether it is arthritis (synovitis, inflammatory synovial fluid, etc.), tenosynovitis, dactylitis (co-existence of both arthritis and tenosynovitis) or enthesitis.

In the case of peripheral enthesitis it is worth mentioning that clinical confirmation might be a great challenge, since inflammation of the enthesis can only be confirmed by imaging: the presence of clinical inflammatory signs near the enthesis can reveal a bursitis, but does not necessarily confirm an enthesitis. The two imaging modalities proposed for peripheral enthesitis diagnosis are ultrasound (US) and MRI. Discordant data have been published about the capability of grey scale US alone to differentiate between enthesis involvement in SpA and in other pathologies. The US (with the use of power Doppler) landmark finding for SpA enthesitis is the presence of abnormal vascularization at enthesis insertion, allowing the differentiation between SpA involvement and other mechanical or metabolic involvements.[23] MRI is currently considered the best imaging modality to identify early axial involvement (spine and sacroiliac joints) in patients with SpA. The typical appearance of peripheral enthesitis on MRI includes soft tissue inflammatory changes and peri-entheseal bone marrow edema, and actually the diagnosis of enthesitis is not likely in case of absence of concomitant bone edema. Thus both imaging techniques present strengths (availability and cost for US, and reliability and bone assessment for MRI) and weaknesses; nevertheless, in the absence of other objective signs of inflammation (such as increased CRP or synovitis), confirmation of enthesitis by either imaging technique seems mandatory. This is particularly important in the light of the potential misdiagnosis with fibromyalgia. Indeed, the presence on clinical examination of tender points, elicited by palpation at specific sites, was part of the 1990 ACR classification criteria for fibromyalgia [24] ; this tender points count is still widely used, but a substantial anatomical overlap between these and many enthesal sites[25] may mislead the physician. A screening for FM in patients with suspected peripheral SpA presenting only with clinical peripheral enthesitis might be useful. The Fibromyalgia Rapid Screening Questionnaire (FiRST) has been proven to be reliable and easy to use in SpA patients, also in clinical practice. [26–28] In doubtful cases, imaging might be helpful: the presence of a high number of involved sites, a high grey-scale score, a high power-Doppler



score in one site and involvement of typical sites (e.g. the Achilles tendon) have been significantly associated with SpA related-enthesitis rather than FM. [29]

Considering other possible explanations why patients have articular symptoms (differential diagnosis) is important: in case of polyarticular joint involvement or in case of an early form of rheumatoid arthritis with oligoarticular manifestations a negative rheumatoid factor and a negative cyclic citrullinated peptide antibodies would make the diagnosis of rheumatoid arthritis less likely.

Especially in case of monoarticular involvement, investigations to rule out crystal-induced arthritis, Lyme disease or septic arthritis (in particular in case of knee involvement) should be performed prior to establishing the diagnosis of peripheral SpA. In DIP involvement, in the presence of psoriasis, differential diagnosis with erosive forms of osteoarthritis (OA) deserves to be mentioned: while degeneration and inflammation may be clearly discernible at the two extremes, in some patients differentiation is extremely difficult, even with available imaging (i.e. plain radiographs). Whether this represents the effect of one disease modifying the other or whether there are other determining factors awaits confirmation. No data on the prevalence of such an overlap are available to date, and this may have implications for the optimal diagnosis and management of both OA and PsA. [30]

### **3. Classification of peripheral spondyloarthritis**

The important difference between diagnosis and classification for SpA and other rheumatic diseases has been dealt with in the past in detail.[31,32] Although there is quite an overlap between classification criteria and parameters used for making a diagnosis of a certain disease classification criteria cannot and should not be used schematically for a diagnostic approach. Classification of SpA historically focused on axial disease and relied on the combination of clinical symptoms plus unequivocal radiographic sacroiliitis according to the modified New York (mNY) criteria presented in 1984. [33] However, to fulfil these criteria, patients had to present structural damage (e.g. radiographic sacroiliitis of the sacroiliac joints (SIJ)), and included only axial symptoms: patients presenting with peripheral symptoms could not be classified as suffering from AS in absence of axial structural damage.

In order to incorporate the different clinical presentations of SpA (including peripheral involvement) others sets of classification criteria were proposed. In the early 1990's Amor and colleagues presented the Amor criteria [34] that included for the first time peripheral features, good response to non-steroidal anti-inflammatory drugs (NSAID), and made the presence of radiological sacroiliitis not mandatory, although kept it weighted to a great extent. However, Amor criteria were not broadly accepted in the European SpA community, and a year later the European Spondyloarthropathies Study Group (ESSG) set of criteria were proposed, which also allowed the fulfilment of the criteria in the absence of axial symptoms. [35] Importantly, SpA was differentiated here for the first time based on the main symptom into axial (patients had to have inflammatory back pain) or peripheral SpA (synovitis, asymmetric or predominantly of the lower limbs) arms.

In 2004, the international group of experts, Assessment of SpondyloArthritis international Society (ASAS), decided to revisit the classification criteria for SpA to permit an earlier diagnosis by including MRI findings in a set of criteria for the first time. Also different from the ESSG criteria, HLA-B27 was added as an important parameter. This approach led to the publication in 2009 of the ASAS classification for SpA [20,36,37] both for axial and peripheral presentations. (Figure 1) Patients fulfill these criteria if they present with the typical clinical picture for peripheral SpA plus one of the associated diseases (shown in in Fig 1), HLA-B27 positivity or sacroiliitis on MRI (in this case on the background of predominant peripheral clinical manifestations!). If this is not the case patients have to have two of the parameters shown in the right part of Fig1 in addition to one entry criterion.

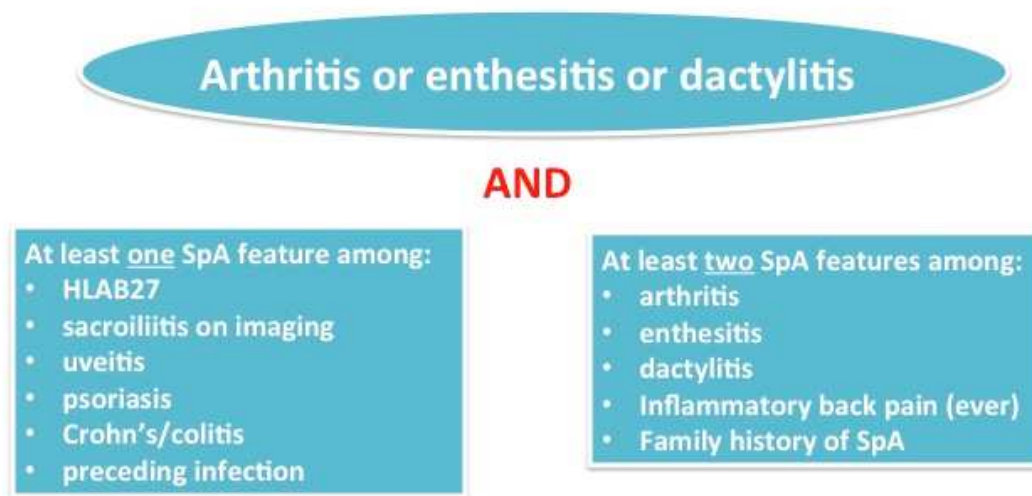


Figure 1: ASAS Peripheral SpA criteria. Adapted from Rudwaleit et al. Ann Rheum Dis 2011;70:25-31

The performances of these criteria have been recently evaluated in a systematic review and meta-analysis, and showed a high pooled specificity (87%) but moderate sensitivity (63%), probably due to the entry criteria (only arthritis) of the studies evaluating the criteria [38]. More recently, the predictive validity of this set of criteria, using as the gold standard the local rheumatologist's 'peripheral SpA' diagnosis after 4 years of follow-up, has been evaluated in the SpA ASAS cohort: the criteria discriminated well between peripheral SpA and no-SpA, yielding a positive predictive value of 89.5%[39]

#### **4. Treatment of peripheral spondyloarthritis**

No specific recommendations for peripheral SpA management have been published. However, the ASAS-EULAR recommendations for axSpA management [3] include

recommendations for management of peripheral manifestations, and EULAR and GRAPPA recently published specific recommendations for PsA management [40,41]

While there are multiple outcome measures for PsA[42], without a final agreement yet on one single score[1], these outcome measures have not been investigated in peripheral SpA. In one analysis of the few available peripheral SpA trials the ASDAS-CRP and the BASDAI, both scores developed and tested repeatedly in clinical trials with axial SpA, performed also well in peripheral SpA trials.[43] For one peripheral SpA trial with adalimumab (see also below) ‘Peripheral SpA Response Criteria’ (including patient’s global, patient’s pain and swollen and tender joints count, enthesitic count or dactylitis count) were developed and performed well [44], however were not yet tested in other trials.

Whereas there are only limited—good quality—data on the treatment of peripheral SpA with csDMARDs, the previous decade has witnessed a wealth of clinical trial data with multiple biological agents, mainly belonging to the class of TNF $\alpha$  blockers and mainly specifically in PsA, particularly the polyarticular forms of PsA. Anthony So and Robert D. Inman extensively cover the treatment of PsA with biologics in the chapter on biologic medications.

#### *Global management of peripheral SpA in general*

Recently EULAR[40] and GRAPPA[41] published updated recommendations for the treatment of PsA, including the use of biologic. The GRAPPA group takes an approach that focuses on the different domains of psoriatic disease, and describes evidence-based treatments for each domain. When instituting a certain treatment, the efficacy should be monitored by the physician with the aim of maximally controlling all aspects of the disease. The EULAR management recommendations mainly deal with peripheral arthritis. A step-up treatment schedule is proposed, starting with NSAIDs, followed by csDMARDs (with methotrexate as anchor drug), then biological agents, usually a TNF blocker. In this algorithm the physician will take prognostic factors, toxicity and inadequate response to the prior level of treatment into account. Usually—when standard (csDMARD) treatments such as methotrexate, sulfasalazine, or leflunomide over a period of 3 to 6 months have failed—the recommendations for the initiation of a TNF blocker require a disease activity with at least one or more swollen and tender joint. Treatment decisions about patients with predominant severe enthesitis or dactylitis have to be made on an individual basis, but there is consensus that biological agents

targeting TNF (after failure of NSAIDs) are probably the first-choice of drugs. In cases of predominant axial involvement, the ASAS/EULAR treatment guidelines for axial SpA should be followed. A clear effect of treatment with bDMARDs or tsDMARDs should be seen after at least 12 weeks of treatment, with rheumatological manifestations exhibiting an earlier response than skin and/or nail disease.

*Specific manifestation's management:*

## **1. Arthritis:**

### ***a. Symptomatic treatment***

#### Non-steroidal anti-inflammatory drugs:

NSAIDs are widely used in daily clinical practice for the initial treatment of any type of arthritis, and are the first level of treatment in the EULAR SpA and PsA treatment algorithms, except in the presence of poor prognosis factors [3,40]. Despite of these recommendations controlled studies assessing efficacy are limited. In the GRAPPA recommendations for arthritis management, NSAIDs are only suggested as concomitant treatment while DMARDs (csDMARDs or TNF blockers (TNFb)) are the first level of treatment [41]. Some studies show that conventional NSAIDs have good efficacy in the treatment of PsA [45,46]; no randomised controlled trial has been performed with Cox-2- specific NSAIDs.

#### Glucocorticoids:

Efficacy and side effects of oral or parenteral glucocorticoids have not been studied systematically in peripheral SpA. Nevertheless, some reported data suggest that (low-dose) systemic steroid therapy is quite frequently used in daily practice[47]. Because dose reduction or withdrawal of glucocorticoids can induce a flare of psoriasis[48], these drugs should be used with caution in patients with PsA and, if necessary, at a low dose and only for a limited time. Intra-articular injections of glucocorticoids are often used in clinical practice, especially for monoarthritis and oligoarthritis.

## **b. Disease modifying antirheumatic drugs**

### Conventional Synthetic Disease-modifying antirheumatic drugs

The use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for peripheral SpA has historically followed the treatment patterns used in RA. CsDMARDs do not play a role in the treatment of axial SpA manifestations, but they have some proven efficacy in peripheral SpA: efficacy data are available for sulfasalazine, leflunomide, and methotrexate [49–52]. However, clinical trials with csDMARDs in peripheral SpA were often non-controlled, used different classification and improvement criteria (making comparison between trials difficult) and included only small numbers of patients. Interestingly, leflunomide was the only drug with proven efficacy in PsA in a double-blind, placebo-controlled study[53].

### TNF-blocking agents

All five TNF-blocking (TNFb) agents approved for the treatment of patients with active axial SpA, have also demonstrated remarkable effectiveness in the treatment of patients with active peripheral SpA. The large majority of these drugs have been studied in polyarticular forms of PsA [54–57], but some others have evaluated the efficacy in other subtypes of peripheral SpA on the arthritis outcome: the Ability-2 trial (adalimumab vs. placebo in patients with non-psoriasis peripheral SpA) showed a significant greater proportion of patients (with swollen joints at baseline) with a null swollen joint count after 12 weeks of treatment in the adalimumab arm ( $p < 0.05$ ) [58]. These positive results were confirmed in another smaller adalimumab trial in patients with peripheral SpA (again presence of psoriasis was an exclusion).[59] While in these studies patients had a rather long disease duration a more recent study investigated the effect of TNF-blockade (with the golimumab) in early forms of the disease ( $\leq 12$  weeks symptom duration). The percentage of patients reaching clinical remission was significantly higher in the golimumab group vs placebo treatment (75% vs 20%, respectively) at week 24. [60]

Contrary to the data with csDMARDs, there is convincing evidence that TNF-blocking agents can halt structural damage in peripheral SpA, as shown by stable erosion and joint narrowing scores of the radiographs of hands and feet in patients treated with a TNF-blocker, compared with further progression in the placebo group, in polyarticular PsA forms.[61] However, no studies have evaluated radiographic progression in other subgroups of pSpA.

### *New biological agents, and other agents*

Ustekinumab, a human monoclonal antibody with high affinity for the p40 subunit of IL-12 and IL-23 has proven its efficacy in the treatment of polyarticular forms of PsA in several RCT against placebo [62,63]. Furthermore, pooled data of these two trials have demonstrated a beneficial structural effect of the drug.[64] No studies have evaluated its efficacy on other subgroups of peripheral SpA patients. but post-hoc analysis of these two trials in the so-called “spondylitis subgroup”, i.e. the subgroup of patients with a diagnosis of spondyloarthritis according to the physician, suggested a slower radiographic progression of peripheral joints in patients treated with the active drug.[65]

Multiple anti-IL-17 agents have been and are being investigated in PsA, but no data yet on other forms of peripheral SpA. Recent publications on the use of secukinumab and ixekizumab —both monoclonal antibodies targeting the IL-17 pathway—and of brodalumab, an IL-17 receptor antagonist, have demonstrated remarkable efficacy on signs and symptoms, but also on radiographic progression inhibition in polyarticular forms of PsA[66–70].

Similar to TNF blocker studies, in trials with ustekinumab and IL-17 inhibitors continuation of previous csDMARD treatment (usually methotrexate) was allowed, and the observed level of response was similar in patients receiving biological drug monotherapy, compared with those receiving the combination with a csDMARD.

Over recent years, small molecules inhibiting intracellular signalling pathways have entered the therapeutic field of RA, with tofacitinib and baricitinib , orally administered JAK inhibitors, being the first of this new therapeutic class having received marketing approval in Europe for the treatment of moderate-to-severe RA. Phase III studies with tofacitinib confirm also its efficacy compared to placebo in patients with csDMARD failure in polyarticular forms of PsA [71] but also in patients with TNFi failure[72], with significantly greater ACR20 response rates in the treatment group. To date, no studies have evaluated its effect on structural progression in these polyarticular PsA forms nor its efficacy in other subgroups of peripheral SpA patients.

Apremilast, another small molecule inhibiting phosphodiesterase 4, has shown moderate efficacy in a number of clinical trials in PsA, but has not been evaluated in other peripheral forms of SpA[73].

## **2. Enthesitis:**

### ***a. Symptomatic treatment***

#### **Non-steroidal anti-inflammatory drugs:**

Evidence suggests that NSAIDs can improve the symptoms caused by enthesitis and are the first level of treatment in the EULAR axial SpA- and PsA- and GRAPPA-PsA treatment algorithms. [3,40,41]

#### **Glucocorticoids:**

Efficacy and side effects of oral or parenteral glucocorticoids have not been studied in peripheral SpA in a controlled fashion. Local injections of glucocorticoids are often used in clinical practice, [74] for peripheral enthesitis, but only a few studies have evaluated its efficacy. [75] Recommendations regarding these injections differ: ASAS/EULAR indicate that local injections with glucocorticoids may be an option to treat arthritis and enthesitis[3], whereas the American College of Rheumatology (ACR) advise against peri-tendon injections of Achilles, patellar, and quadriceps tendons [76]. However, both scientific societies acknowledge the lack of direct evidence endorsing this specific recommendation.

### ***b. Disease modifying antirheumatic drugs***

Conventional Synthetic Disease-modifying antirheumatic drugs have failed to prove any efficacy on peripheral enthesitis[40,41] and are therefore not recommended.

Only few studies have evaluated TNFi effect on peripheral enthesitis : a RCT in patients with NSAID-refractory and MRI-proven persistent heel enthesitis comparing etanercept vs. placebo confirmed a significantly greater improvements in disease activity ( PGA : -37.6 versus -11.6 (p=0.007)) and local heel pain (-36.7 versus -13.1 (p=0.022)), while no significant changes were observed in the MRI findings (bone marrow edema) between groups. [77] In the ABILITY-2 trial, [58] adalimumab was superior to placebo in decreasing the enthesitis count .



A pooled post-hoc analysis of « spondylitis subgroup » of patients from the PSUMMIT-1 and -2 trials for ustekinumab [65] confirmed also a greater decrease in the number of patients with peripheral enthesitis after 24 weeks of treatment in the subgroup of patients receiving ustekinumab.

### 3. Dactylitis:

As in patients presenting with peripheral enthesitis, NSAID are the initial treatment choice, despite the absence of specific studies. [3,40,41]

Most of the (limited) evidence regarding treatment of dactylitis comes from trials in patients with polyarticular PsA. In a systematic review of dactylitis associated with psoriatic arthritis, csDMARDs were found to be ineffective, while several biologic agents, including the TNFi and ustekinumab were found likely to be effective. [78] Also, data from secukinumab studies have proven to be beneficial for dactylitis in patients with polyarticular PsA.[67]

### 4. Treatments for specific subgroups of axial SpA

While the majority of antibiotic trials have failed to show an efficacy in patients with reactive arthritis one study showed that a combination of azithromycin plus rifampicin given over 6 months was superior to placebo in PCR-positive Chlamydia induced reactive arthritis. [15] An association between inflammation of the gut mucosa and peripheral rheumatic manifestation has been described in IBD. [79]. Therefore it can be assumed that any treatment aiming at the healing of the gut mucosa will have an effect on rheumatic manifestations, although this has not been investigated by controlled trials. The large amount of clinical trials in PsA (with a strong focus on biological therapies) have been dealt with in more detail above.

### Summary

Peripheral spondyloarthritis refers to spondyloarthritis with predominant peripheral (arthritis, enthesitis or dactylitis) involvement, and its prevalence, even within the whole group of spondyloarthritis, has not been well studied yet. Diagnosis can be challenging, particularly in the absence of extra-articular manifestations such as uveitis, psoriasis or inflammatory bowel disease. Disease activity measurement should always include assessment of objective signs of inflammation, particularly in the presence of enthesitis, mainly due to the potential

misdiagnosis with fibromyalgia tender points. Several recommendations for management/treatment of psoriatic arthritis have been published but none specifically for peripheral SpA in general. NSAIDs and glucocorticosteroids are the first step of treatment in all peripheral manifestations, while csDMARDs seem only efficacious in arthritis. Several biologics and tsDMARDs (TNFi, antiIL17, JAK-inhibitors) have been proven to be efficacious in peripheral involvement in PsA, but studies on peripheral SpA are rare.

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