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Peripheral spondyloarthritis: What have we learned?

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A B S T R A C T

The peripheral spondyloarthritis (pSpA) entity remains poorly defined in comparison with axial SpA and psoriatic arthritis, as the clinical symptoms have low specificity, the biological markers are virtually lacking, and dedicated randomized controlled trials in this specific indication remain scarce. In addition, clinical similarities between pSpA and psoriatic arthritis (PsA) have been described, partly explained by a resemblance in the pathophysiology of both entities. Thus, diagnosing pSpA can be challenging because of the overlap with other entities and the absence of a specific test or imaging study that can definitively diagnose the condition.

The aim of this review is to summarize the current understanding of pSpA, its epidemiology, physiopathology, clinical diagnosis, and classification criteria. In addition, we present patient-reported outcomes used in pSpA clinical studies, available evidence on therapies, and future directions.

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Introduction

Breakthrough improvement in the understanding of spondyloarthritis (SpA) has been witnessed in the past couple of decades, with an enhanced definition of the phenotype, clinical presentation, and therapies in this widely heterogeneous group of diseases.

The Assessment of SpondyloArthritis international Society (ASAS) has consecrated the classification of SpA patients into two categories according to the main clinical musculoskeletal symptom: predominantly axial (axSpA) and predominantly peripheral (pSpA) [1,2], with significant consequences on the treatment algorithm [3]. Although significant overlaps exist between these two categories, a recent cluster analysis of the peripheral manifestations in SpA (PerSpA) cohort, a worldwide cohort of 4465 SpA patients from 24 countries, has confirmed this classification, which made clinical sense again [4].

However, the peripheral SpA (pSpA) entity remains poorly defined in comparison with axSpA and psoriatic arthritis (PsA), as the clinical symptoms have low specificity, the biological markers are virtually lacking, and dedicated randomized controlled trials (RCTs) in this specific indication remain scarce [5,6]. Nevertheless, studies have shown that pSpA carries a prominent disease burden which contrasts with under-treatment compared with other SpA entities [7].

This review aims to summarize the current understanding of pSpA, its epidemiology, physiopathology, clinical diagnosis, and classification criteria. In addition, we present patient-reported outcomes used in pSpA clinical studies, available evidence on therapies, and future directions.

The evolving concept of peripheral spondyloarthritis

A debate about lumping the SpA subtypes altogether or splitting them has been going on for several years, and the pros and cons of each approach are still broadly discussed [8–10]. Current trends lean toward individualizing homogeneous entities, especially when major therapeutic decisions need to be made.

Peripheral SpA encompasses peripheral articular involvement, enthesitis, and dactylitis. Across the disease course, patients can have a single peripheral feature or an overlap among the three.

First, peripheral arthritis has mostly an oligo- or polyarticular pattern (44.3% and 44.0% in the PerSpA cohort, respectively), with a few patients (11.7%) having a monoarticular disease [11]. Regarding the joint location, the peripheral pattern is associated with arthritis involving both the upper and lower extremities, whereas the axial pattern is mostly associated with lower extremity involvement [4,11]. In addition, there is some controversy about whether root joint disease, i.e., the involvement of hip and shoulder joints associated with SpA, should be considered axial or peripheral involvement. However, a recent post hoc analysis of the PerSpA study showed that hip involvement resembled more axial involvement, with young age at onset, and a high prevalence of HLA-B27, whereas shoulder involvement resembled more peripheral involvement, with a later age at onset, less HLA-B27 positivity and more dactylitis and enthesitis [12].

Second, in enthesitis, the differential diagnosis with fibromyalgia can arise in a significant number of cases. Fortunately, the general context of the disease, the inflammatory nature of the pain, and the advances in imaging, mainly musculoskeletal ultrasound, and magnetic resonance imaging, are key to the correct identification of SpA-related enthesitis [13,14].

Third, with regard to dactylitis, the clinical diagnosis is often straightforward. Although the sensitivity of this manifestation is low (15.3% of all SpA patients in PerSpA, 23.1% in pSpA and 37.0% in PsA), it is nevertheless associated with a high specificity making its presence highly suggestive of pSpA [11]. As dactylitis is a typical feature of PsA, some might argue that pSpA is just PsA without psoriasis (*sine psoriase*). However, a comparative review showed that the difference between the two entities goes beyond semantics. In this review, pSpA represented a more inclusive term compared to PsA *sine psoriase* when used in clinical studies and was associated with a higher prevalence of male gender, HLA-B27 positivity, enthesitis, and involvement of large joints of the lower limbs, whereas PsA *sine psoriase* was associated with a higher prevalence of HLA-Cw6, dactylitis and involvement of hand distal interphalangeal joints [12]. Moreover, another post hoc study from the PerSpA cohort showed that the presence of psoriasis had an impact on the clinical characteristics of pSpA. In this analysis, patients with psoriasis were older, with less HLA-B27 positivity, and had a longer diagnostic delay and a higher

frequency of dactylitis and enthesitis than patients without psoriasis. However, pSpA patients without psoriasis were less frequently treated with biological disease-modifying anti-rheumatic drugs (b-DMARDs) despite a similar disease burden as compared with patients with psoriasis [15].

In the near future, the use of artificial intelligence and big data can be a real paradigm shift in the early diagnosis and treatment algorithm of all SpA categories. However, methodological and ethical issues still need to be addressed before implementing the new technologies in daily practice [16,17].

Epidemiology of peripheral spondyloarthritis

The worldwide prevalence of pSpA in the general population is poorly documented. Most epidemiological data are available from general SpA cohorts, where the relative proportion of pSpA can be estimated within the global SpA entity.

In the PerSpA study, which included consecutive patients with any subtype of SpA, 57% of the patients had peripheral joint disease, including 36% of the patients with axSpA as a main disease. In addition, 44% had enthesitis, and 15% had dactylitis [11]. When asking the treating rheumatologist to select a single main diagnosis for a patient, 10% of all patients with SpA were considered as having pSpA as the main diagnosis (433/4185). Of those, 62% had pure pSpA (270/433), i.e., without PsA and axSpA, compared with 58.1% of patients with pure PsA and 75.2% with pure axSpA. As for the 38% (163/433) of patients with a combined form of pSpA, 75.5% were combined with axSpA (123/163) and 25.1% with PsA (41/163). Consequently, pure pSpA constituted 6.4% of the whole SpA population (270/4185) [7]. Patients with pure pSpA had a higher disease burden compared to those with pure PsA and pure axSpA, as documented by multiple patient-reported outcomes (PROs) but were treated less with b-DMARDs.

In another SpA cohort, Comorbidities in SpA (COMOSPA), including 3985 patients with SpA from 22 countries, the proportion of pSpA was 14%, based on the ASAS classification criteria [18]. In other European studies, such as the Belgian Be-Giant early SpA cohort, the Spanish Esperanza SpA cohort, the Dutch SpA cohort, and the French GAZEL cohort, the pSpA proportion ranged from 22.8% to 28.5% of the whole SpA group [19–22]. In these cohorts, overlap with the other SpA entities was possible.

As for the geographic distribution, analysis of the PerSpA study showed that pure pSpA was more frequent in the Middle East and North Africa region and Asia (9% and 8% of all SpA, respectively) and less frequent in Europe and North America (3.6% of all SpA) [7].

Physiopathology

The clinical similarities between pSpA and PsA are explained by a resemblance in the pathophysiology of both entities.

The pathognomonic feature of pSpA is enthesitis, which can result from repeated mechanical overloading in some cases. It is hypothesized that the threshold for triggering entheseal inflammation is substantially lower in patients with pSpA than in the general population, allowing the development of enthesitis with little or no mechanical force [23]. However, the reason why the threshold for the development of enthesitis in these patients is lower remains unclear. One possible explanation includes genetic factors such as polymorphisms in interleukin 23 receptor (IL-23 R) leading to enhanced and prolonged immune activation [24,25] with the consequent disruption of the epithelial barrier function, resulting in exposure to microbial stress and immune response [26].

New evidence confirmed that IL-23 has a key role in the development of enthesitis. This interleukin is derived from macrophages and dendritic cells, and its overexpression activates T cells residents in the entheses that express IL23R, triggering the enthesitis. The majority of these resident T cells are $\gamma\delta$ T cells, which are at the crossroads of innate and adaptative immunity. In addition, these $\gamma\delta$ T cells represent one of the most important cellular sources of IL-17 and tumor necrosis factor (TNF). In fact, the role of the IL-23/IL-17-axis in PsA has been confirmed by the successful treatment of monoclonal antibodies targeting these cytokines, although no specific clinical trials have been developed in pSpA [5]. The production of IL-17 seems to be a crucial step in augmenting the inflammatory response in the entheses, since it acts as an amplifier of enthesitis and induces the production of other cytokines and mediators by resident mesenchymal cells, which can trigger neutrophil migration and activation [27–29]. In addition, IL-23 is responsible for promoting the expression not only of IL-17 but also of IL22

in enthesitic T cells. Although these interleukins act together, their functions are completely opposite: IL-17 promotes bone erosion and loss, while IL-22 is the predominant cytokine and is responsible for bone remodeling and formation.

Genetic factors also play an important role in the pathophysiology of the pSpA. Human Leucoyte Antigen (HLA)-B27 is present in 17–62.3% of patients with pSpA [20].

There are three accepted hypotheses about the role of HLA-B27 in the pathophysiology of SpA [30]. The first concept, known as the 'arthritogenic' peptide theory, suggests that HLA-B27 presents certain peptides to specific immune cells. This presentation can potentially lead to an autoimmune response, causing symptoms of axSpA. The theory proposes that the gut microbiome, specifically certain organisms that normally exist without harm, could contribute to the production of multiple autoantigens, thus triggering the autoimmune response. The second concept is the homodimerization theory, which states that HLA-B27 chains have the ability to combine with identical chains, forming homodimers. These homodimers can be recognized by certain immune cells such as natural killer cells and $CD4^+$ T cells. The recognition of these homodimers may activate and polarize these immune cells towards a T-helper 17 phenotype, potentially contributing to the development of axSpA. The third concept is the unfolded protein response (UPR) theory. HLA-B27 is synthesized in an intracellular organelle named endoplasmic reticulum (ER). Compared to other HLA types, B27 has a longer period of synthesis within the ER, while the frequency of protein folding alterations is higher. These "misfolded" HLA-B27 that are retained within the ER induce the UPR leading to the production of high levels of IL-23.

Clinical presentation and diagnosis

Overall, the clinical presentation of pSpA can be diverse and may overlap with other forms of inflammatory arthritis [7].

pSpA typically manifests as an oligoarthritis, usually in an asymmetric pattern where the larger joints of the lower limbs are commonly involved, enthesitis or dactylitis in order of frequency [5]. Similarly, when peripheral manifestations occur in patients diagnosed with axSpA, the most frequently found pattern is that of asymmetric oligoarthritis of the lower limbs in large joints [31], in fact it is one of the entry classification criteria of the European Spondylarthropathy Study Group (ESSG) [32]. On the other hand, in PsA, even though a higher frequency of oligoarthritis is also observed [33], we find that arthritis in the upper limbs and small joints predominates, being one of the most important phenotypic manifestations that differentiate it from pSpA [11].

Enthesitis is a common feature of SpA [34]. The pattern of enthesitis can vary depending on the subtype of SpA. In pSpA, enthesitis can affect more frequently the insertion sites of tendons and ligaments in the peripheral joints, such as the knees, ankles, and wrists. Instead, in axSpA, enthesitis primarily affects the insertion sites of tendons and ligaments in the spine and sacroiliac joints. However, both types of enthesitis can be found in both pSpA and axSpA [35]. In PsA, enthesitis can affect both the peripheral and axial joints [36].

Regarding dactylitis, it is considered a hallmark clinical feature of PsA (16–49%) [37]. The prevalence of dactylitis in pSpA is lower and not as characteristic as in PsA [6].

As in the entire group of SpA, in pSpA, extra-musculoskeletal manifestations (EMMs) such as uveitis, psoriasis and Crohn's disease or ulcerative colitis can be found and are part of its classification criteria [2]. Uveitis is the most frequent EMM in SpA [38]. The ASAS-PerSpA study found that the occurrence rate of acute anterior uveitis (AAU) was comparable between individuals with axial (21.6%) and peripheral SpA (17.3%) [6]. It has been observed that HLA-B27 positivity is the most relevant factor linked to AAU risk in SpA patients, especially in patients with pSpA [39]. Psoriasis is the most prevalent EMM in PsA, and there is a natural overlap between pSpA and PsA. The presence of psoriasis has an impact on the clinical characteristics of pSpA, treating less frequently with b-DMARDs those with pSpA [15]. Finally, it is notable that the prevalence of inflammatory bowel disease (IBD) is higher in patients with pSpA (16%) than with axSpA (5%) [40].

Diagnosis of pSpA can be challenging because no specific test or imaging study can definitively diagnose the condition. Apart from the lack of a biomarker, the identification of pSpA is challenging due to its clinical similarities with other conditions, including within the SpA category [6]. Diagnosis is usually based on a combination of clinical evaluation, imaging studies, and laboratory tests.

Within the clinical evaluation, a meticulous search in the personal and family history for SpA of musculoskeletal manifestations (back pain, arthritis, enthesitis or dactylitis) and EMMs (psoriasis, uveitis or inflammatory bowel disease) stands out along with a detailed physical examination [5].

Among the imaging tests to perform in the search for the diagnosis of pSpA are radiography, MRI, and ultrasound. The introduction of sacroiliac MRI revolutionized the early diagnosis of axSpA, observing sacroiliitis before structural damage occurred [41]. However, it has been demonstrated that some patients with pSpA may suffer from asymptomatic sacroiliitis. In fact, in the CRESPA clinical trial it was observed that 35% of patients with pSpA had sacroiliitis on MRI, but only 7 out of 60 patients reported having experienced inflammatory back pain in their past medical history [42]. MRI is also useful for objectively studying inflammation in entheses [43] and MRI inflammation index of peripheral joints and entheses is a promising outcome measure [44].

Another technique to quickly and non-invasively visualize entheses is ultrasound. It is a cost-effective tool that can provide real-time visualization of the enthesis, enabling accurate diagnosis and monitoring of enthesitis in SpA [45]. Several studies have shown the usefulness of ultrasound in the assessment of enthesitis in SpA as an outcome measure [46–48]. Both the visualization of the entheses by ultrasound or MRI will allow us to differentiate entheses suggestive of fibromyalgia from those produced by SpA. Clinically they would be indistinguishable without the use of an imaging test [49].

It is known that the prevalence of HLA-B27 is higher in patients with axSpA than with pSpA [50,51], but it represents an important genetic marker for its diagnosis and classification. The presence of HLA-B27 in patients with pSpA has been associated with earlier disease onset and higher axial involvement, tarsitis and uveitis [52].

Among the laboratory tests to be requested, C-reactive protein (CRP) stands out for both diagnosis and monitoring of the disease. In the ASAS-PerSpA study, the CRP values were high in axSpA (49.8%), pSpA (48%), and PsA (40.1%) [11].

Classification criteria

Several sets of criteria have been proposed and used in clinical studies to define and classify pSpA.

The Amor criteria were developed in 1990 and are based on a series of clinical, radiological, and laboratory symptoms/signs. The classification of SpA is made if the sum of the criteria points is equal to or greater than 6 [53]. Nearly simultaneously, the ESSG criteria were developed in 1991 and are based on the presence of inflammatory low back pain or synovitis (asymmetric or predominantly in lower extremities) along with additional clinical features or radiological criterion (psoriasis, enthesitis, urethritis, IBD or radiographic sacroiliitis). A diagnosis of SpA is made if the patient has at least one of the major criteria and at least one additional clinical feature [32]. Both criteria have similar sensitivity (Amor 88.5% and ESSG 86.6%) and specificity (Amor 91.9% and ESSG 91.1%), with the Amor criteria having greater sensitivity as the entry criterion is not essential and some of the main symptoms, such as uveitis, can be skipped by ESSG criteria but can be founded by Amor criteria [54].

A few years later, the ASAS group proposed to classify the patients according to the clinical presentation: predominantly axial SpA (includes Ankylosing Spondylitis -axSpA- and non-radiographic axial SpA) and predominantly peripheral SpA. This differentiation was made due to the need to recognize their different clinical presentation, treatment, and prognosis, improving the previous criteria (Amor and ESSG) based on the entire spectrum of SpA [1,55].

In 2009, the ASAS group defined the classification criteria for axSpA thanks to the advent of sacroiliac MRI, which allowed early diagnosis of sacroiliitis and the development of the term non-radiographic axial spondyloarthritis (nr-axSpA) [1].

In 2011, the ASAS group defined the classification criteria for pSpA. A patient can be classified as peripheral SpA if they have one of the peripheral features (arthritis, enthesitis, or dactylitis) plus at least one or two additional clinical features that are defined, in the absence of axial symptoms. The new ASAS classification criteria for pSpA seem to work better than the ESSG (sensitivity 62.5%, specificity 81.1%) and Amor criteria (sensitivity 39.8%, specificity 97.8%) [2].

In 2006, an international group of experts in PsA developed a set of classification criteria used for the diagnosis of PsA known as CASPAR criteria (Classification Criteria for Psoriatic Arthritis). The

CASPAR criteria consist of established inflammatory joint disease (joint, spine, or entheseal) with at least three points from the following features: evidence of current psoriasis (score of 2), a personal or family history of psoriasis, psoriatic nail dystrophy, negative test result for RF, dactylitis or radiographic evidence of juxta-articular new bone formation [56]. A patient with joint manifestations (arthritis, enthesitis, dactylitis) with or without psoriasis may meet both the CASPAR and ASAS criteria for pSpA. It has been observed that the ASAS pSpA classification criteria are more inclusive as they encompass EMMs as well as HLA-B27 and sacroiliitis [12]. However, it is a matter of debate whether SpA is a single disease with variable expression or whether they are separate diseases with shared clinical features [8]. A standardization of scientific terminology is necessary to develop treatment and response strategies and design clinical trials.

It should be noted that the clinical diagnosis is based on the clinical pattern, while classification criteria are used to group patients with similar characteristics together for research and treatment purposes and should not be used schematically for a diagnostic approach [57].

Patient-reported outcomes

Patient-reported outcomes (PROs) are health status measures based on patient self-report, such as pain, function, and quality of life [58]. PROs are important in evaluating pSpA because they provide information on the patient's perspective on the impact of the disease on their daily life, allowing monitoring the patient and seeing the response to treatment. Most of the instruments used to assess outcome measures have been validated in axSpA but not in pSpA [59]. In controlled trials, as well as in monitoring patients in clinical practice, there is a need to define the optimal measures for disease activity and clinical response.

Peripheral SpondyloArthritis Response Criteria (pSpARC40) were developed as a response criterion specifically for pSpA on the first clinical trial of treatment for pSpA (ABILITY-2), which compared adalimumab (ADA) vs placebo. The PSpARC40 were defined as $\geq$40% improvement ($\geq$20 mm absolute improvement) from baseline in the visual analog scale (VAS) scores for patient's global assessment (PGA) of disease activity and PGA of pain, and $\geq$40% improvement from baseline in at least one of the following features: 1) swollen joint count and tender joint count, 2) total enthesitis count or 3) dactylitis count [60] (Table 1). While these response criteria may be valuable in clinical studies, they may not be as useful in routine clinical practice. This is because there is no initial visit to compare against, and the criteria do not provide specific information on the severity of disease activity or the identification of different disease states [61].

Other outcome measures used in studies were the improvement in the patient global assessment of disease activity (PtGA) used in the TIPES trial [62] and the definition of clinical remission as the absence of peripheral arthritis, enthesitis, and dactylitis used in the golimumab CRESPA trial [44].

Beckers et al. [63] conducted a study that looked at three composite measures (DAPSA, PASDAS, and ASDAS) in patients with pSpA, with the aim of evaluating their validity and discrimination in real-world clinical practice. DAPSA (Disease Activity in Psoriatic Arthritis) is an outcome measure used to assess disease activity in people with PsA. It includes the assessment of tender and swollen joint counts, patient and physician global assessment of disease activity, and C-reactive protein (CRP) level [64]. DAPSA has been shown to be a valid and reliable measure of disease activity in PsA and is commonly used in clinical

Table 1
Outcome measures and their parameters.

	PGA disease activity	PGA pain	TJC	SJC	Enthesitis	Dactylitis	Inflammatory markers
pSpARC40	+	+	+	+	+	+	
DAPSA	+	+	+	+			+
PASDAS	+	+	+	+	+	+	+
ASDAS	+	+					+
MDA	+	+	+	+	+		

pSpARC40: Peripheral SpondyloArthritis Response Criteria; DAPSA: Disease Activity in Psoriatic Arthritis; PASDAS: Psoriatic Arthritis Disease Activity Score; ASDAS: Ankylosing Spondylitis Disease Activity Score; MDA: Minimal Disease Activity.

trials and clinical practice to monitor disease activity over time and to assess the effectiveness of treatments [65]. PASDAS (Psoriatic Arthritis Disease Activity Score) was developed as part of an international Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) exercise [66]. It is a composite score that includes assessments of tender and swollen joint counts, patient and physician global assessment, Leeds enthesitis index, tender dactylitis count, the physical component of the Short Form (SF) 36 Health Survey, and level of CRP [67]. The DAPSA and PASDAS, which were designed for PsA, performed well for pSpA [63]. ASDAS (Ankylosing Spondylitis Disease Activity Score) is a composite score used to assess disease activity in people with axSpA that includes assessments of back pain, patient global assessment, peripheral joint swelling, duration of morning stiffness and CRP or erythrocyte sedimentation rate (ESR) levels [68]. ASDAS has acceptable concurrent validity and demonstrated good discriminatory ability in patients with pSpA in two randomized controlled trials, ABILITY-2 and Tnf Inhibition in PEripheral SpondyloArthritis (TIPES) in pSpA [59].

MDA (Minimal Disease Activity) it is a composite measure used as an outcome measure in the assessment of PsA that evaluates disease activity based on the presence or absence of specific criteria, including measures of joint and skin disease, physical function, pain, patient global assessment, and tender and swollen joints [69]. Its difficulty to apply in patients with pSpA lies in the evaluation of psoriasis, which is not suitable for a patient who does not have psoriasis. That is why modified MDA has been developed using 5 of 6 criteria in peripheral SpA (excluding psoriasis). It appears to be a valid, discriminative measure to assess treatment differences in patients with peripheral SpA [70].

Treatment

Due to the low prevalence of pure pSpA, the poor definition of the disease, and the scarcity of validated outcome measures, randomized controlled trials in this indication are scarce, and we report here four available studies, all with tumor necrosis factor inhibitors (TNFi), followed by management recommendations.

First, Paramarta et al. compared adalimumab 40 mg every two weeks to placebo in the TIPES trial comprising 40 patients with pSpA, fulfilling the ESSG or Amor criteria without axSpA or PsA, with the primary end point represented by the improvement in patient's global assessment of disease (PGA). At week 12, ASDAS inactive disease and BASDAI50 responses were met in 42% in the adalimumab versus 0–5% in the placebo group ($p = 0.001$ and $p = 0.008$, respectively). However, 55% of the patients in the adalimumab group and 25% of those in the placebo group were positive for HLA-B27 [61].

Second, the ABILITY-2 trial compared adalimumab 40 mg to placebo in 165 patients with non-psoriatic pSpA, fulfilling the ASAS pSpA criteria and who did not have a prior diagnosis of psoriasis, PsA, or axSpA, and had an inadequate response or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs). At week 12, the pSpARC40 was 39% in the adalimumab arm compared to 15% in the placebo arm ($p = 0.006$). HLA-positivity was found in 67% of the patients in the adalimumab arm and 56% in the placebo arm. Improvement in other outcomes was also greater in the adalimumab group compared to the placebo group, including PGA, BASDAI, ASDAS, enthesitis scores [59].

Third, the CRESPA (Clinical REmission in peripheral SPondyloArthritis) trial evaluated golimumab 50 mg every four weeks versus placebo in 60 patients with very early active pSpA (12 weeks symptom duration or less), fulfilling the ASAS pSpA criteria, and naïve to cs-DMARDs. At week 24, 75% of the patients treated with golimumab were in remission, defined by the absence of arthritis, enthesitis or dactylitis, compared to 20% in the placebo arm ($p < 0.001$). The pSpARC40 response was 50% in the golimumab arm compared to 15% in the placebo arm ($p = 0.011$). Rescue medication, available at 12 weeks, was necessary in 50% in the placebo group opposed to only 10% in the golimumab arm. Notably, 50% of the patients in the golimumab and 65% in the placebo arm were positive for HLA-B27, and 42% of the patients in the golimumab and 40% in the placebo arm had psoriasis [41].

Finally, a trial evaluating the impact of treatment on enthesitis was perfomed by Dougados et al., in patients with SpA regardless of the disease presentation (axSpA vs. pSpA). They evaluated etanercept 50 mg weekly in 24 patients with SpA according to the Amor criteria and heel enthesitis proven by MRI (HEEL study). Over 12 weeks, significant improvements were reported in patients treated with etanercept compared to placebo in several PROs: PGA for disease activity, heel pain, and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) function. Notably, 67% had axial involvement, and

75% were HLA-B27 positive in the etanercept group, compared with 58% and 67% in the control group, respectively [71].

Specific guidelines for pSpA were published by the National Institute for Health and Care Excellence (NICE) in 2021 (Table 2). They recommended starting with a trial of two conventional synthetic DMARDs (cs-DMARDs), in parallel with NSAIDs or glucocorticoids injections to control symptoms. In case of failure of conventional therapy, apremilast (a phosphodiesterase (PDE)4 inhibitor) and TNFi were proposed as second-line therapies. As third-line therapies, interleukin 17 inhibitors (IL-17i), ustekinumab (an IL-12/23 inhibitor), Janus Kinase inhibitors (JAKi), and guselkumab (an IL-23 inhibitor) were recommended after at least one b-DMARD failure [72].

Otherwise, recommendations to treat pSpA are often extrapolated from PsA management recommendations, such as the EULAR 2020 [73] or the GRAPPA 2021 [74] recommendations or extracted as individual statements from axSpA recommendations, such as the ASAS-EULAR management recommendations [75]. The current ASAS-EULAR recommendations also advise beginning a course of NSAIDs as a first-line agent, taking risks and benefits into account. Local glucocorticosteroid injections are recommended as well. In case of failure of this initial strategy, cs-DMARDs, namely sulfasalazine, are proposed, although few studies with Methotrexate and Leflunomide were also identified. In patients

Table 2
Treatment recommendations for peripheral spondyloarthritis, including individual recommendations extracted from axial spondyloarthritis recommendations, and compared with recommendations for the management of psoriatic arthritis.

	NICE 2021 Peripheral SpA	ASAS-EULAR 2023 Axial SpA	GRAPPA 2021 PsA	EULAR 2020 PsA
First Line	NSAIDs (Adjunct therapy) Local or intramuscular corticosteroids	NSAIDs Local corticosteroid injections	NSAIDs	NSAIDs (Adjunct therapy) Local or intramuscular corticosteroids
Second Line	csDMARDs (Two trials)	csDMARDs (Mainly Sulfasalazine)	csDMARDs (Mostly MTX) [Skip this step if axial disease, IBD, uveitis)	csDMARDs (MTX preferred for skin) [Skip this step if axial disease, enthesitis)
Third Line	TNFi, PDE4i	TNFi or IL17i (current practice), or JAKi [TNFi monoclonal: if recurrent uveitis or active IBD. IL17i: if significant psoriasis]	bDMARDs (TNFi, IL12/23i, IL23i, CTLA4-Ig) or JAKi or PDE4i	bDMARDs: IL17i, IL12/23i if relevant skin involvement TNFi if active axial disease
Fourth Line	IL17i, IL12/23i, or tafacitinib. IL23i: if moderate to severe psoriasis	TNFi, IL17i or JAKi		JAKi or PDE4i

ASAS: Assessment of SpondyloArthritis international Society, b-DMARDs: biologic disease-modifying anti-rheumatic drugs, cs-DMARDs: conventional synthetic disease-modifying anti-rheumatic drugs, EULAR: European League of Associations for Rheumatology, GRAPPA: Group For Research And Assessment Of Psoriasis And Psoriatic Arthritis, IBD: Inflammatory Bowel Disease, IL: interleukin, JAKi: Janus Kinase inhibitor, MTX: Methotrexate, NICE: National Institute for Health and Care Excellence, NPF: National Psoriasis Foundation, NSAIDs: Non-Steroidal anti-inflammatory Drugs, PDE4i: Phosphodiesterase 4 inhibitor, PsA: Psoriatic Arthritis, SpA: Spondyloarthritis, TNFi: Tumor Necrosis Factor inhibitor.

Table 3
Peripheral spondyloarthritis research agenda.

Peripheral Spondyloarthritis Research Agenda
Estimate the true prevalence of pSpA in different populations.
Elucidate pathophysiological mechanisms.
Develop diagnostic tools: role of artificial intelligence?
Validate classification criteria in different populations around the world.
Conduct dedicated randomized controlled trials to validate therapies in pure and combined forms of pSpA.

with persistently high disease activity despite these conventional treatments, biological DMARDs (b-DMARDs), such as TNFi or IL-17i or JAKi, should be considered, although current practice would be to start with TNFi or IL-17i. However, the absence of psoriasis or axial involvement may sensibly impact the outcome of a specific therapy.

Future directions/research agenda

Despite recent advancements in our current understanding in pSpA, mainly thanks to global cohorts, many areas of unmet research needs persist (Table 3).

- Epidemiology: there is still a need to estimate the true prevalence of pSpA in different populations.
- Pathophysiology: why do patients develop pure pSpA while other develop it in combination with axSpA?
- Diagnosis: can we benefit from new artificial intelligence technologies to provide a better characterization/definition/diagnosis of the disease?
- Classification criteria: there is a need to validate classification criteria in different populations around the world.
- Treatment: more dedicated RCTs are needed to validate therapies in pSpA and different disease patterns: with or without psoriasis, with or without axSpA.

Practice points

- The prevalence of pSpA worldwide has not been well documented due to the significant overlap between pSpA and PsA.
- The diagnos of pSpA may be challenging because of the overlap with other entities and the absence of a specific diagnosis test.
- Enthesitis represents a common feature in pSpA, in which the interleukin 23 (IL 23) plays a key role in the development of this manifestation.
- Randomized controlled trials in pSpA are scarce, and only Golimumab and Adalimumab have demonstrated efficacy in this disease phenotype.

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