The holistic management of peripheral spondyloarthritis: focus on articular involvement in patients with inflammatory bowel disease

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Summary

Objective. To provide a comprehensive overview of peripheral spondyloarthritis (pSpA), focusing specifically on its occurrence and management in patients with inflammatory bowel disease (IBD).

Methods. An exhaustive literature search was conducted in PubMed, Embase, Cochrane Database of Systematic Reviews, and Google Scholar to identify relevant studies on pSpA in IBD patients. Titles, abstracts, and full-text articles were screened for relevance. Data on study design, patient characteristics, diagnostic criteria, main findings, and conclusions were extracted from selected articles. Study quality was assessed using appropriate checklists. Information was synthesized narratively to summarize current understanding.

Results. pSpA is the most common extraintestinal manifestation of IBD, with a median prevalence of 16%. It worsens quality of life and requires collaboration between gastroenterologists and rheumatologists for optimal diagnosis and treatment. Several "red flags" guide appropriate specialist referral of IBD patients with suspected pSpA. Once the diagnosis is confirmed, the choice of therapy depends on IBD phenotype and patterns of articular/axial involvement. Anti-tumor necrosis factor (TNF) drugs are first-line biologics, with interleukin (IL)-12/23 and IL-23 inhibitors as alternatives for anti-TNF failure. Small molecules like apremilast and Janus kinase inhibitors also have utility. Recommended treatment algorithms exist, but more randomized controlled trials are needed.

Conclusions. Early identification of pSpA is crucial in IBD patients to enable timely intervention, prevent structural damage, and minimize disability. A multidisciplinary, holistic approach addressing musculoskeletal and extra-musculoskeletal manifestations is key to optimal patient outcomes.

Introduction

Spondyloarthritis (SpA) is a group of chronic inflammatory diseases that affects the axial skeleton and peripheral joints with a possible association with other articular and extra-articular manifestations [enthesitis, dactylitis, psoriasis, uveitis, inflammatory bowel diseases (IBD), and comorbidities].

Historically, classification criteria for SpA were published in the early '90s (Amor criteria and European Spondyloarthritis Study Group) based on the key clinical features with variable specificity and sensitivity. They provided valuable criteria for implementation in clinical trials and practice (1).

Approximately 10 years ago, the Assessment of SpondyloArthritis International Society (ASAS) made revisions to the phenotypical approach, commonly referred to as the "SpA concept". They validated a more comprehensive classification system for axial SpA (axSpA) and peripheral SpA (pSpA) (2). The classification of pSpA, which was previously somewhat neglected, encompasses various clinical manifestations characterized by arthritis, enthesitis (inflammation of the tendons and ligaments that attach muscles to bones), and/or dactylitis. These manifestations can occur with or without axial involvement and share a common genetic background (2) (Figure 1).

Besides these musculoskeletal symptoms, pSpA patients frequently show extra musculoskeletal manifestations, such as acute anterior uveitis, psoriasis, or IBD, and various comorbidities, mak-

ing managing patients more complex (3). pSpA encompasses different entities, such as reactive arthritis and psoriatic arthritis (PsA). Because of its higher incidence and prevalence, this latter is the archetype of pSpA, with its own classification criteria (Classification Criteria for Psoriatic Arthritis) (4). Patients with PsA have a substantial clinical burden due to skin, articular, and extra-articular involvement in which different "subsets" of disease should be identified. Articular involvement, skin and nail involvement, enthesitis, dactylitis, axial disease, and related conditions are the key clinical features to be evaluated for a holistic approach. Furthermore, the early identification of PsA could be possible since it occurs mainly in patients with a personal or familial history of psoriasis, leading to timely diagnosis and treatment, which is crucial to prevent long-term structural damage and disability (5-7).

Epidemiology of peripheral spondyloarthritis

The prevalence of SpA is estimated to be between 0.9% and 1.7%, with variations due to methodological differences. However, few studies have used the ASAS classification criteria to differentiate between SpA subgroups. The relative prevalence of pSpA has been found to be similar across different European studies, ranging from 22.8%-28.5% (8). Two recent international studies, endorsed by the ASAS, examined patients with SpA on a global scale. The first study, known as the Comorbidities in SpA (COMOSPA) study, involved 3,985 SpA patients from 22 countries (9). In this study, 56.4% of the patients exhibited peripheral joint involvement, and 14% met the ASAS pSpA classification criteria. It is noteworthy that patients who met both the ASAS axSpA and pSpA criteria were exclusively categorized in the axial group (9). Moreover, the presence of psoriasis and the absence of human leukocyte antigen (HLA)-B27 were identified as factors associated with the development of peripheral symptoms.

However, in the more recent study focused on peripheral manifestations in SpA, known as the PerSpA study (10), which included 4,465 SpA patients from 24 countries, only 9.7% of the patients were classified as pSpA. This lower prevalence is likely due to the definition of pSpA as the "main diagnosis" in this particular study. Including patients with overlapping features would probably increase the prevalence, as 78% of the 4,465 patients had experienced at least one peripheral musculoskeletal manifestation. Peripheral disease was reported in 57%, enthesitis in 44%, and dactylitis in 15%. When considering the different regions of the world, the highest prevalence of peripheral joint disease (80%) was found in Latin America (8, 10).

The prevalence of HLA-B27 in predominant pSpA varies between 27% and 47%. However, the diagnostic and prognostic significance of this genetic risk factor has been inadequately investigated beyond the scope of axSpA. It is estimated that genes within the major histocompatibility complex account for less than 50% of the heritable aspects. HLA-B27 has a low prevalence in the non-axSpA, which indicates that it does not define disease diagnosis (11).

Methods

The objective of this narrative review is to provide a comprehensive overview of pSpA with a particular focus on its occurrence in patients with IBD. To this end, a rigorous approach was employed to identify, select, and review pertinent literature, as shown below.

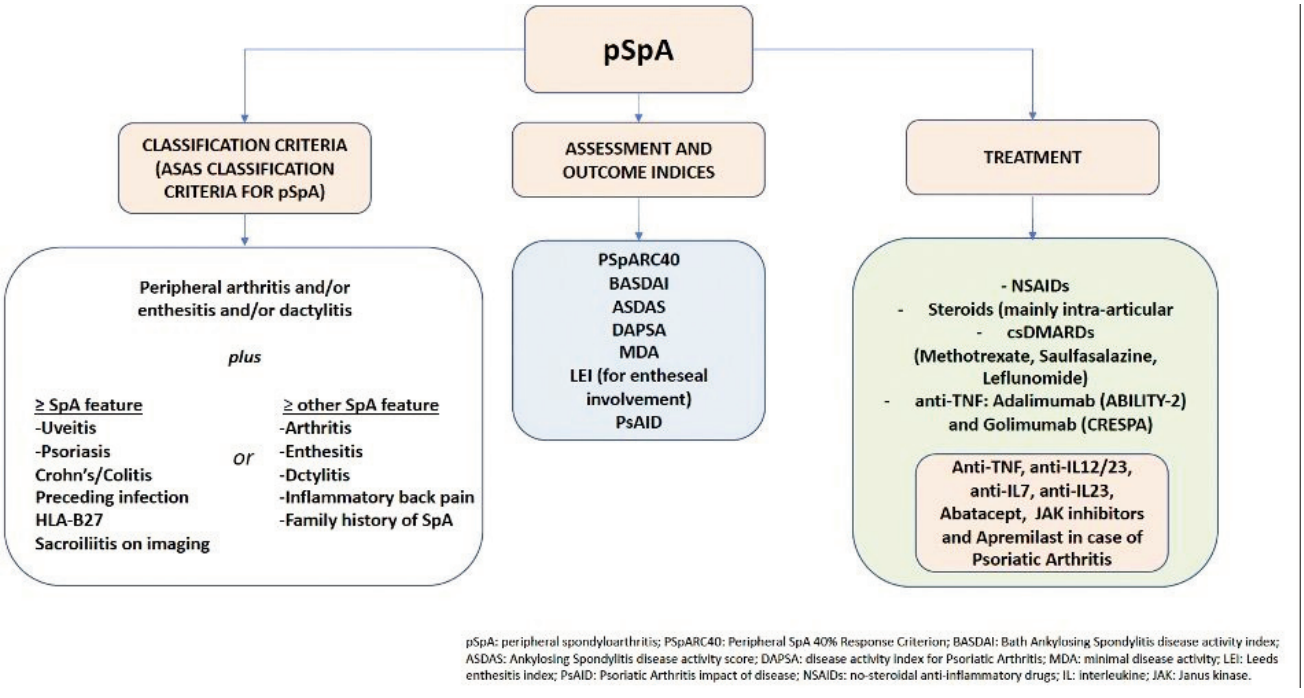

Figure 1. Overview of peripheral spondyloarthritis.

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Literature search

An exhaustive search of PubMed, Embase, Cochrane Database of Systematic Reviews, and Google Scholar databases was conducted. The search was limited to articles published in English. Keywords and phrases used in the search included "peripheral spondyloarthritis", "pSpA", "inflammatory bowel disease", "IBD" "Crohn's disease" "ulcerative colitis" and combinations of these.

Study selection

Initially, titles and abstracts of articles identified in the literature search were screened for relevance. Full-text articles were then retrieved for those that appeared to meet the review criteria and were scrutinized in detail. The focus was on original research articles, clinical trials, observational studies, and reviews that provided insights into the pathophysiology, clinical manifestations, diagnosis, and treatment of pSpA in IBD patients.

Data extraction

From each selected study, relevant data were extracted, including study design, sample size, patient characteristics, diagnostic criteria used for pSpA and IBD, main findings, and conclusions.

Quality assessment

The quality of the included studies was assessed using appropriate checklists based on the study design. This helped ensure that the review was based on robust and high-quality evidence.

Synthesis of information

The data extracted from the individual studies were synthesized narratively. The review presents an overview of the current understanding of the pathophysiology of pSpA in IBD, discusses the clinical manifestations and diagnostic challenges, and reviews the current approaches to treatment.

Holistic treatment strategy in peripheral spondyloarthritis

In 2014, Smolen et al. first developed the concept of a treat-to-target (T2T) strategy to be applied in the whole group of SpA (12), with the aim to improve the management of the disease, which might be implemented in patients with some characteristics (namely joint or skin, depending of the predominant manifestations) (13) to achieve the target of disease remission in all clinical domains.

Due to the complexity of the disease, several composite indices were proposed to identify disease activity status and to assess a condition of low disease activity and remission that encompass all spectrums of the disease (14). The Disease Activity Score for Psoriatic Arthritis and the Minimal Disease Activity indices were, therefore, proposed in the recent T2T recommendation (12, 15). Together with those indices, other instruments could be used to capture the presence of enthesitis, dactylitis, axial involvement, the impact of disease, function, and quality of life, such as the Psoriatic Arthritis Impact of Disease and the Patient Acceptable Symptom State (16, 17). The effect of various outcome measures that evaluate disease activity and treatment response in pSpA is still unknown. The reliability of a dedicated outcome will depend not only on the precise definition of the patient population but also on the availability of valid outcome measures and response criteria. To accurately reflect the typical symptoms of pSpA, such as arthritis, enthesitis, and dactylitis, it might be helpful to develop new composite measures and response criteria specific to pSpA. In the ABILITY-2 trial (18), the first randomized controlled trial involving patients with pSpA who met the current ASAS classification criteria, a novel response criterion for pSpA was introduced. This criterion is known as the "Peripheral SpA 40% Response Criterion" (PSpARC40). The PSpARC40 is defined as a ≥40% improvement from baseline (with an absolute improvement of ≥20 mm) in the Visual Analog Scale (VAS) scores for Patient Global Assessment (PGA) of disease activity and PGA of pain on a 100 mm VAS. Additionally, it requires a ≥40% improvement in at least one of the following measures: i) swollen joint count (76 joints) and tender joint count (78 joints); ii) total enthesitis count; or iii) dactylitis count. The study demonstrated that this newly developed PSpARC40 criterion exhibited good discriminatory capacity in evaluating treatment response in pSpA. It performed well in comparison to other established response criteria, such as the rheumatoid arthritis (RA)-specific American College of Rheumatology response criteria, the axSpA -specific Ankylosing Spondylitis Disease Activity Score (ASDAS)-C Reactive Protein and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), as well as the PGA and physician's global assessment. Currently, the value of the PSpARC criteria, which are specific to pSpA, should be further investigated to determine if they accurately reflect the multiple aspects of the disease.

Overall, due to the multiform nature of PsA and, more in general, pSpA, the management of patients should include the assessment of different disease domains. The recent Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (19), and the European Alliance of Associations for Rheumatology (EULAR) recommendation for the treatment of PsA take into account this complexity (20). Both international groups developed treatment recommendation that includes each disease domain. Moreover, developing new drugs that specifically target key cytokines and intracellular pathways involved in the disease's pathogenesis allows for better control of disease activity and remission in almost all disease domains in axSpA and pSpA. Anti-tumor necrosis factor (TNF), anti-interleukin (IL)-12/23, anti-IL-17, anti-IL-23 biologic drugs, and targeted synthetic Disease Modifying antirheumatic drugs such as anti-phosphodiesterases 4 (PDE4) and Janus kinase inhibitors (JAKi) proved their efficacy and effectiveness in clinical trials and clinical practice (6, 8, 15, 21). All these drugs were effective in the treatment of peripheral arthritis, enthesitis, dactylitis, and skin involvement and the improvement of function and quality of life (6, 8, 15, 21). The possibility to switch or swap between drug classes further increases our therapeutic chance of managing the disease better. Recent studies on IL-17 inhibitors (secukinumab and ixekizumab) and IL-23 inhibitors (guselkumab) and data coming from trials on anti-TNF, showed the efficacy and effectiveness of these drugs, even in the management of the axial disease (5-8, 15, 21-25). However, differences may be seen in the effectiveness mainly for managing specific domains (such as skin) or controlling related diseases such as extra-articular manifestations or comorbidities. Additionally, the influence of comorbidities and associated conditions on the management and treatment of the primary condition should be appropriately acknowledged and addressed. These include conditions like obesity, metabolic syndrome, cardiovascular disease, mental health issues such as depression and anxiety, liver disorders like non-alcoholic fatty liver disease, chronic infections, cancer, bone health considerations like osteoporosis, central sensitization conditions such as fibromyalgia, and issues related to reproductive health. For individual patients, a multidisciplinary and multispecialty evaluation and treatment approach may yield the best results. For these reasons, a holistic approach, considering the complexity

of the disease and its shades endorsed by treatment recommendations, is crucial for comprehensive management. Wherever possible, treatment for an individual with pSpA should be selected to address all active domains of the disease and any related conditions. Treatment may likely be driven by the most severe or impactful domain of disease, particularly where strong evidence of differential efficacy exists (3, 26).

Alongside pharmacological treatment, physical therapy and rehabilitation may play an essential role in managing patients. Nevertheless, holistic management of pSpA involves treating not only the physical symptoms, but also the psychological, social, and emotional impact of the condition. Living with a chronic condition such as pSpA can be challenging and lead to stress, anxiety, and depression. Pain, fatigue, and limited mobility can also affect a patient's sense of self-worth and self-esteem. This results in higher scores on several patient-reported outcomes questionnaires. In the ASAS-COMOSPA study (9), pSpA patients' Bath Ankylosing Spondylitis Functional Index, BASDAI, and Work Productivity and Activity Impairment Questionnaire were all worse than SpA patients without peripheral manifestations, either, arthritis, enthesitis, or dactylitis. Gender also may influence clinimetrics. Benavent et al. found that female gender was associated with higher ASDAS and BASDAI in pSpA patients (27). Interestingly, besides the active research in the context of PsA, no formal recommendations were published for the management of the whole group of pSpA, which remains a "neglected entity" (2).

Peripheral spondyloarthritis and inflammatory bowel disease

SpA represents the most common extraintestinal manifestation (EIM) in patients with IBD (14), with a prevalence that may reach 46% in some cohorts of patients. In a recent review, the median prevalence of axSpA and pSpA in IBD was 5% (range 1-46%) and 16% (range 1-43%) (28). The clinical characteristics of pSpA in IBD are similar to those of pSpA in the general population. The most common symptoms are back pain, sacroiliitis (inflammation of the sacroiliac joints), and enthesitis. There are some sex differences in the perception of disease in pSpA. Women with pSpA are more likely to report pain than men, and they are also more likely to experience other symptoms, such as fatigue and depression. Women with pSpA are also more likely to have comorbidities such as obesity, cardiovascular disease, and metabolic syndrome. Osteopenia and osteoporosis are counterintuitively more frequent in men (29, 30).

The presence of joint pain worsens the quality of life and the work productivity of patients with IBD (31), and the coexisting articular inflammation significantly influences the clinical and therapeutic management of IBD patients: therefore it should be promptly identified. The collaboration between gastroenterologists and rheumatologists is fundamental to guarantee the best diagnostic and treatment strategy in patients with co-existing IBD and SpA. Several clinical clues may help to determine a proper specialist referral. In this regard, a consensus among experts proposed

Red flags in SpA	Criteria classification	Red flags in IBD	Criteria classification
Chronic diarrhoea	Major	Chronic low back pain	Major
Rectal bleeding		Dactylitis	
Perianal fistula/abscess		Enthesitis	
Chronic abdominal pain			
Nocturnal symptoms		Peripheral joint pain / swelling	
Oral aphtosis	Minor	Family history of SpA	Minor
Fever		Psoriasis	
Anaemia		Anterior uveitis	
Family history of IBD		Chest pain	
Weight loss			

Figure 2. Red flags for early referral to gastroenterologists and rheumatologists and for diagnosis of coexisting inflammatory bowel disease (IBD) and spondyloarthritis (SpA).

some "red flags" that may guide clinicians in the early identification of co-existing gastrointestinal and rheumatologic conditions (Figure 2). In IBD patients, chronic low back pain, dactylitis, enthesitis, and peripheral joint pain/swelling should be considered as major criteria for rheumatologic referral in the suspicion of entheropatic SpA, whereas a family history of SpA, psoriasis, anterior uveitis and chest pain represent minor criteria and should be associated (at least three minor criteria in the same patient) or investigated with further tests before referral (32).

Once the diagnosis of co-existing IBD and SpA is confirmed, the gastroenterologist and the rheumatologist should continue to collaborate to settle on the best therapeutic strategy for each patient. The therapy of IBD includes several options, depending on the disease extension and activity, and some of them can be efficacious also in case of articular involvement, i.e., steroids, anti-TNF agents, methotrexate (MTX), ustekinumab and JAKi. The characteristics of SpA, with peripheral or axial involvement, also may influence the type of medical approach. Controlled randomized trials for the treatment of these specific clinical settings have not been realized yet, but several algorithms have been proposed by expert consensus to share specific therapeutic strategies (33-35).

On this basis, we suggest the flowchart in Figure 3.

Pharmacological therapy for peripheral spondyloarthritis

Non-steroidal anti-inflammatory drugs

In treating any type of arthritis, including pSpA, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in clinical practice as a first line of treatment. However, the efficacy of NSAIDs in peripheral arthritis has only been evaluated in studies related to PsA, with some studies showing positive results. Despite a lack of specific studies, NSAIDs are also recommended for patients with peripheral enthesitis or dactylitis (2).

When IBD is in stable remission, a short-term course of selective cycle-oxygenase-2 inhibitors can be allowed for the treatment of active SpA, based on two controlled clinical trials which showed no increased risk of intestinal flare during a 2-week and 3-month course of celecoxib or etoricoxib, respectively (36, 37). The use of traditional NSAIDs should be discouraged in patients with SpA associated with IBD given the risk of intestinal toxicity.

Glucocorticoids

There is limited systematic research on oral or parenteral glucocorticoids' efficacy and side effects in pSpA. However, data from the ASAS-COMOSPA cohort shows that low-dose systemic

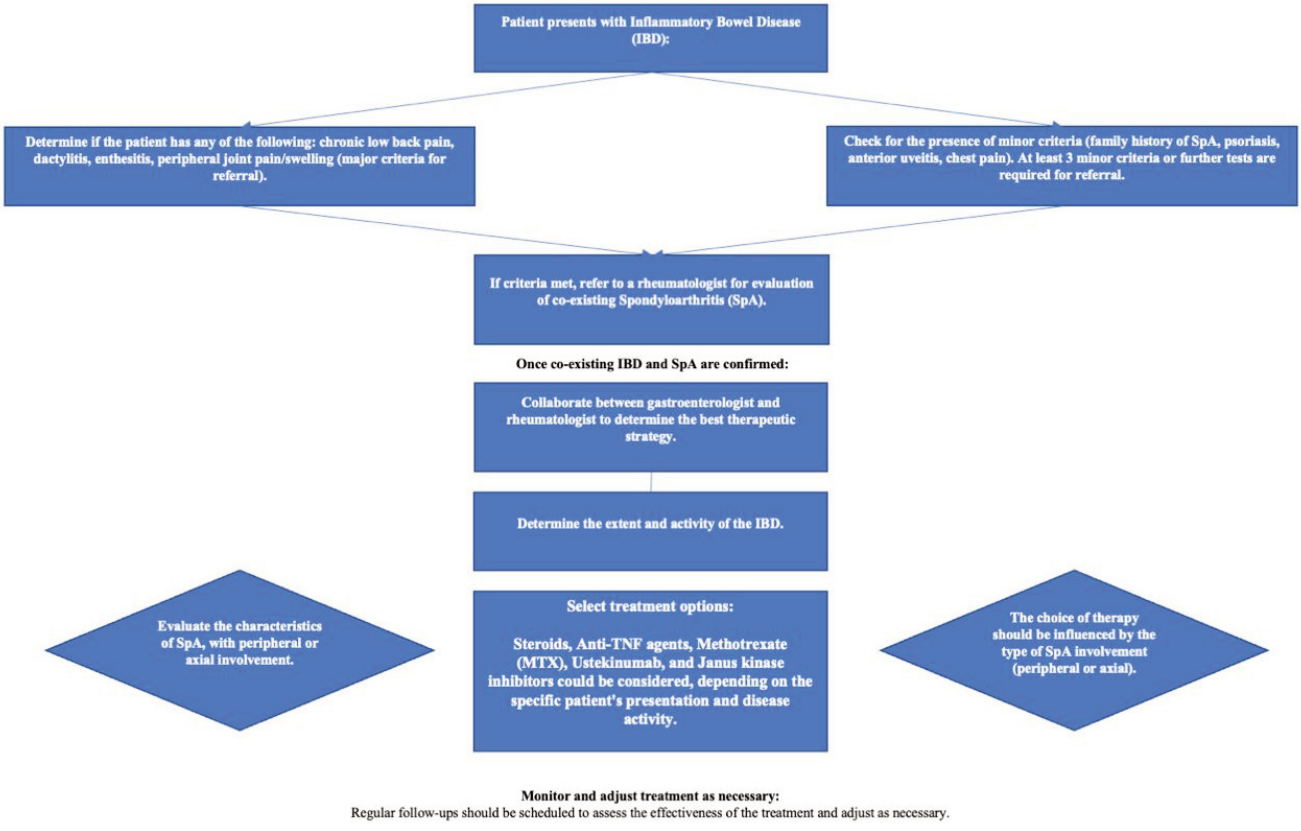

Figure 3. Flowchart referral to rheumatologists.

and intra-articular glucocorticoids are frequently used in practice, particularly for monoarthritis and oligoarthritis (9). In general, in compliance with gastroenterologists' protocols for IBD treatment, there is a trend to avoid oral steroids, also to limit osteoporosis risk and metabolic side effects (35). For patients with recent onset oligoarthritis, an early treatment strategy using intra-articular glucocorticoids followed by sulfasalazine if the patient does not respond has been shown to reduce synovitis 12 months after treatment compared to those only treated with NSAIDs. Local peritendinous glucocorticoid injections may provide benefits for patients with enthesitis, such as at the greater trochanter or the plantar fascia, but only a few studies have evaluated their efficacy.

Conventional synthetic disease-modifying antirheumatic drugs

For patients with pSpA who have persistently active disease due to insufficient response to their initial treatment, a conventional synthetic (cs-) disease-modifying antirheumatic drug (DMARDs) may be prescribed. Options include sulfasalazine (2 g daily), MTX (up to 25 mg once a week), or leflunomide (20 mg daily). Despite the lack of randomized controlled trials specifically for non-psoriatic pSpA, there is evidence of the benefits of using MTX and leflunomide for PsA, and sulfasalazine for ankylosing spondylitis patients with reactive arthritis and peripheral arthritis (2). In 2021, the National Institute for Health and Care Excellence (NICE) published guidelines specifically for pSpA. According to these guidelines, conventional non-biological therapy should be the starting point, with the addition of NSAIDs or corticosteroid injections (either local or intramuscular) to manage symptoms. A trial of two cs-DMARDs is suggested before proceeding to more advanced treatment options. Several options are available in the event of treatment failure but no clear-cut algorithm has been outlined (8). In the case of active IBD associated with pSpA, compared to SpA, the rheumatologists have few more options efficacious on both diseases. First, sulfasalazine can be indicated in place of traditional mesalazine in patients with IBD and associated pSpA or in those with axial involvement and contraindications to anti-TNFs (32, 34). Oral steroids may have a positive impact on the acute phase of both diseases but are not recommended as maintenance therapy. Among immunomodulators, MTX seems to give positive results as a treatment of pSpA and may be useful on coexistent Crohn's disease.

Anti-tumor necrosis factor agents

Anti-TNF drugs represent a class of biologic (b-) DMARDs that have significantly transformed the therapeutic landscape for a variety of inflammatory diseases. The primary mechanism of action of anti-TNF drugs involves the neutralization of the pro-inflammatory cytokine TNF-α (38). TNF-α plays a central role in the pathophysiology of inflammatory responses. It is produced primarily by activated macrophages, but also by a wide range of other cells including lymphocytes, neutrophils, and fibroblasts. TNF-α exerts its effects through binding to two distinct receptors, TNF receptor 1 and TNF receptor 2, which are expressed on the surface of various cell types. Upon activation, these receptors trigger a cascade of signaling pathways that contribute to inflammation, including the activation of nuclear factor κB and mitogen-activated protein kinases, leading to the production of other inflammatory cytokines, upregulation of adhesion molecules, and increased vascular permeability (38). Anti-TNF drugs, which include monoclonal antibodies such as infliximab, adalimumab, golimumab, and certolizumab pegol, as well as the soluble TNF receptor fusion protein etanercept, bind to TNF-α, thereby preventing it from interacting with its receptors. This effectively inhibits the downstream inflammatory signaling cascade. Furthermore, the binding of anti-TNF drugs to TNF-α can lead to the formation of immune complexes that may be removed by the reticuloendothelial system, reducing the amount of active TNF-α in circulation. Consequently, the overall inflammatory response is dampened, mitigating the symptoms and progression of inflammatory diseases. Some studies on anti-TNF showed these drugs' efficacy in managing the disease in randomized clinical trials and paved the way for future research with other mechanisms of action (3). The ABILITY-II trial was the first to use the ASAS criteria to classify patients with non-psoriatic pSpA (18). This study demonstrated that 39% of patients in the adalimumab group achieved the primary endpoint of PSpARC40 response compared to 20% of patients in the placebo group. In this regard, the more recent CRESPA trial showed that very early recognition of disease and initiation of golimumab treatment led to a substantially higher response compared with patients with more established disease (21). Second and of equal importance, the results from the placebo arm did not support the hypothesis that a substantial proportion of patients with early pSpA go into spontaneous clinical remission. At week 24, 75% (30/40) of golimumab-treated patients reached a status of complete absence of arthritis, enthesitis, and dactylitis compared with only 20% (4/20) in the placebo group ($p<0.001$). The status was already achieved as early as week 12 [70% (28/40) vs. 15% (3/20); $p<0.001$]. At week 12, a pSpARC 40%, 50%, and 70% response were observed in 57.5%, 55%, and 50% of patients treated with golimumab vs. 20%, 20%, and 15% in the placebo group (21). Among biologics, anti-TNF agents represent the first option in this setting, preferring infliximab or adalimumab at gastrointestinal doses, whereas the use of etanercept should be discouraged in IBD patients, given the reported risk of intestinal exacerbation. Golimumab is a further anti-TNF option in patients with established diagnosis of ulcerative colitis and SpA, whereas it is not currently approved for treating Crohn's disease (34). Moreover, in patients with SpA and Chron's disease, another therapeutic possibility is the use of certolizumab pegol (39, 40).

Other biologics

Assimilating evidence from PsA, in anti-TNF-refractory patients anti-IL12/23, apremilast, and anti-IL23 are viable therapeutic agents targeting different inflammatory pathways, each with their distinct mechanism of action.

Anti-IL12/23, such as ustekinumab, inhibits both IL-12 and IL-23 by binding to their shared p40 subunit. IL-12 and IL-23 are pro-inflammatory cytokines that play key roles in differentiating and activating T helper 1 (Th1) and T helper 17 (Th17) cells, respectively. By neutralizing the p40 subunit, anti-IL12/23 drugs prevent the downstream signaling and activation of these T cells, thereby attenuating the inflammatory response implicated in various immune-mediated diseases (41).

Ustekinumab is a valid therapeutic option for patients with PsA and concomitant IBD as it is approved for both Crohn's disease and ulcerative colitis. Anti-IL23 agents, like guselkumab, specifically target the p19 subunit of IL-23, a cytokine that is crucial for the expansion and maintenance of Th17 cells. By selectively binding to the p19 subunit, these drugs inhibit the interaction of IL-23 with its receptor, thereby impeding the activation and function of Th17 cells. Consequently, the production of pro-inflammatory cytokines by Th17 cells, such as IL-17, IL-22, and TNF-α, is reduced, leading to the amelioration of inflammation in various immune-mediated diseases.

Guselkumab recently also showed promising results in patients

with Crohn's disease, carrying the potential for treating such disease when concomitant PsA also occurs (42-46). Risankizumab, a humanized IgG1 monoclonal antibody that specifically inhibits IL-23 by binding to its p19 subunit, has proven effective for patients affected with PsA in KEEPsAKE 1 and 2 trials. At the moment it is also approved for the treatment of Crohn's disease (47).

Small molecules

Apremilast is a small molecule PDE4 inhibitor. It acts by increasing intracellular levels of cyclic adenosine monophosphate (cAMP) via inhibition of PDE4, an enzyme that catalyzes cAMP degradation. Elevated cAMP levels modulate the production of pro-inflammatory cytokines, such as TNF-α, IL-23, and IL-17, and promote the release of anti-inflammatory cytokines, such as IL-10. As a result, apremilast exerts its anti-inflammatory effects by downregulating key inflammatory mediators. JAKi downregulate the JAK-STAT signaling pathway, which transmits information from cytokines and growth factors to the cell nucleus, affecting gene expression and cell function. JAKi are used to treat several autoimmune diseases like RA, PsA, IBDs, and alopecia areata.

Either tofacitinib and upadacitinib are approved for PsA and ankylosing spondylitis, with tofacitinib being also indicated for ulcerative colitis and upadacitinib for both Crohn's disease and ulcerative colitis (48).

If conventional therapy fails to manage pSpA, with more than three tender and swollen joints still present, apremilast and TNFi have been suggested as the next steps in NICE guidelines. Should the first and second-line therapies also fail, ustekinumab and JAKi have been suggested as third-line options. A prospective cohort study is currently recruiting IBD patients with associated EIM treated with ustekinumab to specifically investigate its effects on extraintestinal diseases (TENOR study, ClinicalTrials.gov Identifier: NCT03606499). If pSpA remains active despite failure of at least one b-DMARD, guselkumab has been advised as a third-line therapy (8). In patients with pSpA with or without IBD, EULAR recommendations for vaccination do apply to reducing infection risk due to immunosuppressants and aberrant immune response (49).

Conclusions

The management of pSpA, and in particular PsA, is improving thanks to the development of different clinimetrics for assessing patients' disease burden and of new effective drugs and treatment strategies, which allow for better treating those complex entities in all disease domains.

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