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SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

Current Unmet Needs in Spondyloarthritis

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Abstract

Purpose of Review There was a substantial progress in the field of spondyloarthritis (SpA) in terms of understanding disease mechanisms, early diagnosis, and improved treatment. Nonetheless, several unresolved questions and unmet needs do remain.

Recent Findings Although the diagnostic delay in axial SpA is decreasing, it remains one of the longest in rheumatology. Application of referral strategies, as well as correct application and interpretation of imaging finding in the clinical context, is the main key to early diagnosis of axial SpA. Tumor necrosis factor (TNF) alpha and interleukin (IL)-17 represent currently two major treatment targets in SpA, while other promising targets such as IL-23 or IL-6 failed in clinical trials. There is an unmet need for strategy trials to optimize and to individualize treatment in SpA. The role of Janus kinases and their blockade in SpA is still to be explored. TNF blockade showed efficacy in peripheral SpA, and other targets (IL-17 and IL-23) should be investigated in clinical trials. Early, effective, and long-term suppression of inflammation is currently the best method to prevent structural damage progression in the spine in axial SpA, while specific effects of IL-17 blockade and of nonsteroidal anti-inflammatory drugs on new bone formation are still being investigated.

Summary This review summarizes the recent advances in diagnosis and treatment of SpA and discusses the current unmet needs in the field.

Keywords Spondyloarthritis · Diagnosis · Imaging · Pathophysiology · Treatment · Radiographic progression · Unmet needs

Introduction

Spondyloarthritis (SpA) is an umbrella term that covers a group of inflammatory musculoskeletal disorders with shared genetic background (e.g., an association with HLA-B27), pathophysiological mechanisms (e.g., a leading the role of the Th-17 pathway), and common clinical features (involvement of the axial skeleton, a typical pattern of peripheral arthritis,—usually mono- or oligoarthritis with involvement of lower extremities—enthesitis, dactylitis, association with psoriasis, acute anterior uveitis, and inflammatory bowel disease) [1••]. Depending on the leading manifestation, SpAs can be classified as axial (predominant involvement of the axial skeleton—sacroiliac joints and spine) or peripheral (with arthritis, enthesitis or dactylitis dominating the clinical presentation). Axial SpA includes two major forms or stages: the nonradiographic axial SpA (nr-axSpA), i.e., axial SpA without structural damage visible on X-rays of sacroiliac joints and/or spine, and radiographic axial SpA (also referred to as ankylosing spondylitis—AS), i.e., axial SpA structural damage visible on X-rays of sacroiliac joints and/or spine. The entire group of axial SpA is covered by the Assessment of SpondyloArthritis international Society (ASAS) classification criteria published in 2009 [2]. The peripheral SpA group covered by the ASAS classification criteria for peripheral SpA [3] is more heterogeneous and includes reactive arthritis, arthritis associated with inflammatory bowel disease, psoriatic arthritis—PsA (though not all forms of PsA can be classified as SpA due to differences in phenotype), and so-called undifferentiated peripheral SpA.

In this review, we focus on current unmet needs in SpA related to diagnosis, disease mechanisms, and related treatment targets, as well as to structural damage progression in SpA.

This article is part of the Topical Collection on *Spondyloarthritis*

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Unmet Needs in Diagnosis

The mean diagnostic delay in AS has been reported to be around 9 years almost two decades ago [4]. Introduction of the ASAS classification criteria, implementation of magnetic resonance imaging (MRI) in the diagnostic approach [5], and educational efforts improved the situation; however, there is still frequently a gap of several years between the onset of symptoms and the diagnosis of axial SpA. The most recent study conducted in Germany showed a mean diagnostic delay of approximately 5.7 years) median 2.3 years). Importantly, female sex, HLA-B27 negativity, presence of psoriasis, and young age of symptom onset were independently associated with a longer diagnostic delay [6•].

An earlier diagnosis requires early referral of these patients to a rheumatologist. The major challenge is, therefore, the identification of patients with a high probability of axial SpA in a large group of patients with back pain. Axial SpA is responsible for approximately 5% of chronic back pain (i.e., back pain lasting for more than 3 months) cases in the general population; thus, a structured screening/referral approach is required to identify patients with possible axial SpA by a primary care physician or a nonrheumatology specialist. A number of referral strategies have been proposed and tested in the last 20 years [7•]. The following lessons have been learned from these research efforts:

- Any screening/referral strategy is helpful;
- There is no single referral strategy with outstanding performance: the probability of axial SpA increases due to the application of a referral strategy from 5 to 30–40%;
- Simpler strategies perform equally well compared to complex strategies among patients presenting to the rheumatologist with chronic low back pain possibly due to axial SpA;
- The starting point should be chronic back pain with a rather young age of onset (usually below 45 years).

Finally, the ASAS developed recommendations for the early recognition of patients with a higher probability of axial SpA by primary care physicians and nonrheumatology specialists [7•]. According to this recommendation, patients with chronic back pain (duration ≥ 3 months) and back pain onset ≤ 45 year of age should be referred to a rheumatologist if at least one additional SpA parameter is present (e.g., inflammatory character of back pain or HLA-B27-positivity, or sacroiliitis on imaging, etc.). The ASAS referral recommendation represents, therefore, a flexible tool that can be adapted to a local situation with regard to the selection of SpA parameters which are used in addition to the two stem parameters.

Thus, as of today, we have good screening/referral tools but their implementation, meaning increase of SpA awareness among doctors dealing with back pain patients (general practitioners, orthopedists, neurologist, physiatrist, physiotherapy-specialists, etc.), is currently the major problem and the unmet need in the field.

Another current unmet need is the correct use and interpretation of imaging in the clinical context of early diagnosis of axial SpA. X-rays of sacroiliac joints have been used for years for the diagnosis and classification of ankylosing spondylitis, though it is obvious that structural damage in the sacroiliac joints (and, to a further extent, in the spine) results from previous inflammation and normally takes months to years to develop. With the introduction of MRI in the practice of rheumatology, early diagnosis of axial SpA became a realistic aim, since active inflammation in the sacroiliac joints (subchondral bone marrow edema/osteitis [8]) can be recognized immediately after disease onset. In the last years, there is an increasing number of publications reporting a high prevalence of bone marrow edema in sacroiliac joints in healthy subjects without back pain [9, 10]. Also, mechanical problems/degenerative disease often manifest with bone marrow edema in the sacroiliac joints. The current definition of a positive MRI of sacroiliac joints [8] relies largely on the presence of bone marrow edema. However, this definition is intended for use for classification purposes (i.e., not for the primary diagnosis) and it includes also a qualitative aspect—the bone marrow edema must be highly suggestive of SpA, meaning that structural, post-inflammatory lesion should also be taken into account as an important context for interpretation of edema as a manifestation of axial SpA. It is possible that a new commonly accepted and data-driven definition of a positive MRI of sacroiliac joints will be developed that would consider structural changes not only in a quantitative but also in a qualitative way. In any case, we see a need for education of radiologist and especially rheumatologist on the correct interpretation of imaging findings in the axial skeleton.

Needless to say that imaging findings should always be considered in the context of clinical and lab parameters. With that regard, it is important to stress again the differences between the classification and the diagnostic approach. Classification criteria are intended for use in clinical studies to select a homogeneous patient population. A prerequisite for application of classification criteria is a clinical diagnosis of the disease (SpA in our case) and of course exclusion of differential diagnoses. For this reason, classification criteria give a "yes" or "no" answer with a certain level of sensitivity and specificity, which nearly never reach 100%. In contrast to classification criteria, a real diagnostic approach (such as the likelihood ratio approach [11]) operates with a probability of the disease instead of yes/no categorization. Further, in the diagnostic approach—as opposed to classification—negative results of the diagnostic tests are taken into account along with the positive results. Thus, a misuse of the ASAS classification criteria (and the ASAS definition of positive MRI) as a tool for the primary diagnosis should be avoided—this requires continuous educational efforts as well.

Unmet Needs in the Identification of New Treatment Targets

According to the current understanding of disease mechanisms in SpA, the interaction between immune system and microbiome on a certain genetic background (such as presence of HLA-B27) leads to the development of active inflammation (primarily in the sacroiliac joints and in the spine in axial SpA and in peripheral entheseal structures with possible secondary synovitis in peripheral SpA), whereby local mechanical stress seems to be necessary to initiate this process [12]. Molecules and pathways involved in the inflammation would be suitable as "targets" for therapeutic interventions.

Animal models, investigations of peripheral blood, local fluids such as synovial fluid, and tissue samples are used to identify targets for therapeutic interventions. However, it is crucial to prove the importance of such targets through therapy studies. For axial SpA, the detection of tumor necrosis factor (TNF)-alpha-expressing cells in biopsies from the sacroiliac joint was a decisive preliminary work [13] followed by successful treatment studies. However, blocking other potential targets involved in inflammation such as interleukin (IL)-6, IL-1, T cells, or B cells was not effective in axial SpA [14] although preclinical studies had also indicated a possible role of these molecules in the inflammatory process.

In recent years, the IL-23/IL-17 pathway became a target for therapies in various chronic immune-mediated diseases, based on a crucial role of these cytokines for these diseases in animal models. The IL-17 producing T-helper cells (Th17-cells) differentiate in the presence of cytokines IL-1, IL-6, and TGF-ß and are finally stabilized in the presence of IL-23, which is also responsible for the local secretion of IL-17 [15]. Genetic analyses [16], investigations of peripheral blood, and spinal biopsies [17] of axial SpA patients had indicated a possible important role of the IL-23/IL-17 pathway for the pathophysiology of axial SpA. This assumption was further supported by the occurrence of enthesitis in an animal model with overexpression of IL-23 [18]. Furthermore, the good therapeutic response of psoriasis to both IL-17 and IL-23 inhibitors suggested that IL-23 and IL-17 effects are closely related. Treatment studies in PsA and rheumatoid arthritis also showed a similar effect of these two therapeutic principles (moderate effect in PsA and low effect in RA) [14, 19•].

IL-17 inhibition was indeed effective in the therapy of axial SpA (so far only study results on AS published) with the following previously tested and published antibodies against IL-17: secukinumab (monoclonal antibody to IL-17A), ixekizumab (monoclonal antibody to IL-17A), bimekizumab (monoclonal antibody to IL-17A and F), and netakimab (monoclonal antibody to IL-17A) [20]. By indirect comparison (in the absence of true head-to-head studies), a similar level of efficacy can be achieved with IL-17 inhibitors as with the TNF inhibitors. These two drug classes have been approved in many countries around the world for the treatment of axial SpA (with some variations in nonradiographic and radiographic forms of axial SpA) not responding to nonsteroidal anti-inflammatory drugs (NSAIDs). According to the current ASAS and European League Against Rheumatism (EULAR) treatment recommendations, TNF and IL-17 inhibitors (referred to as biological disease-modifying antirheumatic drugs—bDMARDs) are placed on the same level in the treatment algorithm, though the current practice (that might change over time) is to start with TNF inhibitors [21••]. In patients who are nonresponders to anti-TNF therapy, the efficacy of IL-17 blockade could also be shown, although the response was generally lower compared to anti-TNF-naïve patients [22, 23].

It is of great clinical relevance whether the same patients or different patients respond to TNF- and IL-17-inhibition, whether potential responders can be identified prior to treatment initiation, what the optimal first choice of a bDMARD is, what the optimal strategy of switching in a case of a nonresponse, and, finally, whether a combination of both treatments is an option in some of the patients [19•]. Thus, strategy trials are needed in order to define the optimal first-line bDMARD in axial SpA as well as the optimal treatment strategy in the case of primary or secondary nonresponse.

In contrast to IL-17, IL-23 blockade failed to show a clinically relevant efficacy in placebo-controlled studies in axial SpA: in three studies with ustekinumab directed against the p40 protein of IL-23 and thus also against the cytokine IL-12 [24] and in one study with risankizumab directed against the p19 protein of IL-23 and, therefore, specifically blocking this cytokine [25]. IL-23 is predominantly produced by dendritic cells and monocytes, which are abundantly present in the skin and whose IL-23 secretion is presumably responsible for the stimulation of Th17 cells as well as other IL-17-producing cells. The situation in the subchondral bone marrow, the primary site of inflammation in axial SpA, is more complex, and IL-17 secretion could probably be achieved by direct contact of local mesenchymal cells with T cells without the mediation of IL-23 [26]. IL-17 can also be produced by various non-Th17 cells such as CD8+ T cells, γδT cells, innate lymphoid type 3 cells, and NK cells. It has also been described that neutrophils and mast cells express IL-17, which is presumably not produced by themselves but only absorbed exogenously when secreted by other cells [27, 28]. For most of these cell types, it has been described that IL-17 can be secreted without IL-23 stimulation [29•, 30]. Thus, the hypothesized independence of IL-17 production from IL-23 in bone marrow in patients with axial SpA should be further investigated in order to explain uncoupling of IL-23 and IL-17 effects observed in axial SpA treatment trials.

The preclinical data on the crucial role of IL-23 and IL-17 in the development of enthesitis—the hallmark of all forms of

SpA—has raised questions about a potentially higher efficacy of IL-23 or IL-17 blockade in enthesitis as compared to other treatment options, first of all—TNF blockade. Available data derived mostly from secondary analyses of studies in axial SpA and PsA indicate that enthesitis responds well to therapy with TNF and IL-17 inhibitors [14] but no conclusion about superior/inferior efficacy can be drawn. The failure of anti-IL-23 therapies in axial SpA raises the question of whether these therapies are also ineffective in enthesitis. Secondary analyses of PsA studies indicate good efficacy of IL-23 inhibitors in enthesitis [31]. Recently, a prospective and randomized (but not blinded) trial with the IL-23 inhibitor ustekinumab and with the TNF inhibitor adalimumab was published, in which ustekinumab was superior to adalimumab with respect to the effect on enthesitis [32]. Thus, randomized double-blind head-to-head studies with enthesitis as the primary endpoint are still needed in order to differentiate available treatment options. Currently, a head-to-head trial with IL-17 (secukinumab) and TNFα inhibitor (adalimumab) in PsA is underway (ClinicalTrials.gov ID: NCT02745080), but enthesitis is only a secondary endpoint in this trial.

Closely related to the enthesitis topic is the question of the efficacy of bDMARDs in patients with peripheral SpA without axial involvement and without psoriasis. This group of patients covered by the ASAS classification criteria for peripheral SpA [3] has been almost neglected in the past. Two investigator-initiated studies in peripheral SpA with TNF inhibitors adalimumab and golimumab have been performed, both with positive results [33, 34]. However, only one phase II/III study with a TNF inhibitor adalimumab has been conducted for this indication [35]. Although the superiority of adalimumab over placebo had been demonstrated for the combined primary endpoint and for its components including peripheral arthritis and enthesitis, no attempt to obtain regulatory approval for the indication has been made. Since patients with peripheral SpA without signs of axial involvement and without psoriasis do not have any effective approved treatment options, phase 3 clinical studies with TNF, IL-23, and IL-17 inhibitors are urgently needed.

Janus kinases (JAKs) responsible for the intracellular signaling via activation of STATs (signal transducer and activators of transcription) [36] and, therefore, interfering with a number of inflammatory pathways, is another potential treatment option in SpA, though the role of JAKs in the pathogenesis of SpA has not adequately studied so far. JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase (TYK)2 members. Currently, a number of JAK inhibitors are under investigation for the indication of axial SpA.

Tofacitinib is a pan-JAK inhibitor that has been approved for the treatment of rheumatoid arthritis and PsA. Tofacitinib demonstrated superiority to placebo in a phase II study in patients with AS [37]. A phase III study with tofacitinib in AS is ongoing now (ClinicalTrials.gov ID: NCT03502616). Filgotinib is a selective JAK1 inhibitor that also showed positive results in a phase II study in AS [38]. These positive results should be confirmed in phase III studies and mechanisms of anti-inflammatory activity of JAK inhibitors in axials SpA should be explored. In the case of a positive outcome of phase III studies, questions related to the place of JAK inhibitors in the treatment algorithm of axial SpA, related to specific predictors of response, to switching strategies and possibility of a combination with bDMARDs would be raised similar to the question related to IL-17 blockade. Another JAK1 inhibitor upadacitinib is being currently evaluated in a phase IIb/III randomized controlled trial in patients with active AS (ClinicalTrials.gov ID: NCT03178487). Concerning baricitininb (a JAK1 and 2 inhibitor approved for rheumatoid arthritis), there is currently no clear information about ongoing or planned clinical studies in axial SpA.

Unmet Needs in Retardation of Structural Damage Progression

In addition to the reduction of symptoms caused by active inflammation, such as pain and stiffness, prevention or retardation of structural damage development in the spine (new bone formation resulting in ankylosis, frequently referred to as radiographic spinal progression) is also important for the management of axial SpA. Available data suggest that inflammation is essential for the development of subsequent new bone in the spine: radiographic spinal progression is positively associated with elevated C-reactive protein (CRP), active inflammation on MRI, and with the level of the Ankylosing Spondylitis Disease Activity Score (ASDAS), which includes not only patient-reported outcome parameters but also CRP [39••]. Inflammation in the subchondral bone marrow can lead to the development of repair tissue (granulation tissue) if the inflammation is not suppressed early and effectively. The granulation tissue then gives rise to osteoblasts, which form new bone [39••].

It has been postulated that a therapeutic prevention of ossification can be achieved by early and long-lasting therapy of the inflammation or by a direct effect on osteoblasts, which are uncoupled from the presence of inflammation at a later stage. In order to follow such a development, MRI is currently the best method, despite limitations in the detection of new bone formation. The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) based on conventional radiographs of the cervical and lumbar spine is currently the most commonly used measure for the assessment of spinal structural damage in axial SpA.

In the first studies with TNF inhibitors in AS, the 2-year mSASSS progression rate in patients treated with this drug class was not significantly different from the historical control group [40–42]. In the most recent study, in which patients with axial SpA were treated over 4 years with the TNF inhibitor

certolizumab, radiographic progression in the spine in the first 2 years was similar to patients without anti-TNF therapy, but a significant reduction of such progression was observed between year 2 and 4 [43].

These data were confirmed in several observational studies indicating that at least 4 years of treatment in rather advanced disease are needed in order to reduce progression of structural damage in the spine [44, 45•, 46]. Further, initiation of anti-TNF treatment within the first 10 years of disease was associated with a reduction of radiographic spinal progression as compared to a later treatment onset [46]. Finally, radiographic spinal progression was significantly lower when the ASDAS status of inactive disease (i.e., remission) was achieved during anti-TNF therapy [45•]. This latter observation is especially important in the light of the treat-to-target recommendations declaring remission as the main treatment target in axial SpA [47••]. A confirmation of this association linking symptomatic and structural outcomes of anti-inflammatory therapy in a prospective trial is one of the current unmet needs in axial SpA (Table 1).

TNF-alpha has no clear effect on osteoblast activation; therefore, such TNF blockers can only be effective via inhibition of inflammation. However, there is currently a continuing discussion as to whether this might be different for IL-17. The effect of IL-17 on the bone can primarily be considered destructive, similar to TNF. However, under certain circumstances, IL-17 may also have a stimulating effect on osteoblasts [48••]. Whether such an effect plays a role in axial SpA and therefore whether IL-17 inhibition, in addition to the effect on inflammation and disease activity, can also retard new bone formation needs further investigation. Therapy with the IL-17 inhibitor secukinumab in patients with AS over a total of 4 years resulted in a somewhat slower progression by indirect comparison to older studies with TNF blockers discussed above [49]. An ongoing head-to-head trial comparing secukinumab to adalimumab in terms of inhibition of radiographic spinal progression over 2 years should bring clarity to the question if there is a clinically meaningful effect associated specifically with IL-17 blockade (ClinicalTrials.gov ID: NCT03259074).

NSAIDs still represent the first-line therapy in the drug treatment of axial SpA with good efficacy against pain and stiffness. However, NSAIDs could also have an inhibitory effect on bone formation via inhibition of prostaglandin production. In fact, an earlier study over 2 years showed that in AS patients who had been treated continuously (daily intake) with an NSAID, in this study predominantly with celecoxib, the radiographic spinal progression was delayed compared to the group of patients who were treated with an NSAID on demand [50]. Unfortunately, this result could not be confirmed in a very similar study [51], in which diclofenac and not celecoxib was chosen as the main study drug. These results have raised the question of whether the inhibition of ankylosis might be a celecoxib-specific effect. Another important and unsolved question is whether a combination of a TNF blocker

Table 1 Summary of the current unmet needs in spondyloarthritis

Area	Unmet need/research question	Possible solution(s)
Early diagnosis	Long diagnostic delay especially in axial form of SpA	Application of referral strategies for early identification of patients with axial SpA
	Uncertainty with imaging (and especially MRI) interpretation in the diagnostic approach	Trainings of rheumatologists on imaging application and interpretation for early diagnosis of axial SpA
Treatment targets	Uncertainty regarding the optimal treatment strategy with bDMARDs in axial SpA (first choice, switching, predictors of response, possible combinations)	Strategy trials in axial SpA
	The role of Janus kinase inhibitors in axial SpA	Phase III and strategy trials
	Lack of effect of IL-23 blockade in axial SpA	Studies of local immunopathology in the spinal structures; identifying the cellular source of IL-17 in SpA
	Comparative efficacy of bDMARDs in enthesitis	Head to head trials with enthesitis as a primary outcome
	Lack of approved therapeutic options in peripheral SpA	Phase II/III trials with TNF, IL-17, IL-23 and Janus kinases inhibitors
Inhibition of structural damage progression in the spine	The role of the treat-to-target approach for inhibition of structural damage in axial SpA	A prospective treat-to-target study with a structural outcome
	Inhibition of structural damage progression in advanced disease with IL-17 blockade or NSAIDs	Prospective controlled trails

with an NSAID might be more effective than a monotherapy with TNF blocker in terms of inhibition of structural damage progression in the spine. A multicenter randomized study that is currently being conducted in Germany comparing monotherapy with a TNF blocker (golimumab) with a combination of TNF blocker plus continuous treatment with an NSAID (golimumab plus celecoxib) should answer both these questions [52] (ClinicalTrials.gov ID: NCT02758782).

Conclusion

Application of referral strategies, as well as correct application and interpretation of imaging finding in the clinical context, is the key to the early diagnosis improvement in axial SpA. There is an unmet need for strategy trials to optimize and to individualize treatment in SpA. The role of Janus kinases blockade in SpA is still to be explored. Interventional trials are needed in peripheral SpA. It should be clarified in ongoing studies if there is a specific effect of IL-17 blockade and of NSAIDs on radiographic spinal progression in axial SpA which goes beyond their anti-inflammatory effects.

Compliance with Ethical Standards

Conflict of Interest Joachim Sieper reports grants and personal fees from Abbvie, Janssen, MSD, and Pfizer and personal fees from Lilly, Novartis, Roche, UCB, and Sun Pharma.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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