Spondyloarthritis: From disease phenotypes to novel treatments
Paramarta, Jacky

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General introduction

Spondyloarthritis: from unifying concepts to improved treatment

Jacqueline E. Paramarta, Dominique Baeten

Department of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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ABSTRACT

Spondyloarthritis (SpA) is a chronic immune-mediated inflammatory disease with diverse phenotypic manifestations including spondylitis, arthritis, enthesitis and extra-articular manifestations (psoriasis, uveitis, inflammatory bowel disease). The common genetic risk factors, the strong familial aggregation and the overlapping immunopathology suggest that these different phenotypic manifestations share common pathogenic pathways. This concept is further strengthened by the good clinical response of all different SpA manifestations to TNF-blocking therapies. However, the phenotypic diversity of SpA is still a major challenge in properly diagnosing, classifying and monitoring the disease and may lead to undertreatment of less typical SpA cases such as undifferentiated SpA. The optimal use of current treatments and the development of novel therapies, including compounds targeting the IL-23/IL-17 axis, thus requires a detailed understanding of both the clinical presentation and the underlying pathogenic pathways in SpA.
INTRODUCTION

SpA is one of the most prevalent forms of chronic inflammatory arthritis, affecting approximately 0.5-1.5% of the Western population. The clinical presentation of the disease is dominated by inflammation that can affect the axial skeleton (spine and sacroiliac joints), peripheral joints (especially the large joints of the lower extremities) and extra-articular sites such as the eye (uveitis), skin (psoriasis) and gut (IBD), resulting in highly heterogeneous phenotypes of disease in different patients. Moreover, this inflammation can be accompanied by different degrees and types of structural damage, ranging from extensive bone destruction to new bone formation and even complete ankylosis of axial and peripheral joints. In combination, the different types and degrees of tissue inflammation and structural damage lead to a variety of different phenotypes in SpA. Nevertheless, the strong common genetic background, as evidenced by its high heritability, suggests a common origin of the different SpA phenotypes. The most important genetic risk factor, HLA-B27, has been known now for 40 years. More recently, genome-wide association studies have revealed additional genetic links in SpA, e.g. genetic risk variants of interleukin-23 receptor (IL-23R) and endoplasmic reticulum aminopeptidase 1 (ERAP-1), which may give further clues to the pathogenesis of this disease. Besides the genetic background, the different SpA manifestations also share the same key environmental triggers such as microorganisms and mechanical stress. Therefore the key question arising here is whether the different disease manifestations of SpA are driven by the same pathogenic mechanisms and, if so, whether therapeutic targeting of these public pathways can lead to clinical benefit in the different SpA subforms. On the contrary, if the different disease manifestations are not driven by the same pathogenic pathways, one should delineate sharply which private pathway is pathophysiologically and therapeutically relevant in which subset of SpA patients.

WHERE DOES IT ALL START?

McGonagle et al. proposed a unifying pathophysiological concept for SpA based on the idea that specific tissues may be particularly sensitive to mechanical triggers. They proposed that the primary lesion of SpA is enthesitis (inflammation at the attachment sites of ligaments, tendons and joint capsules to the bone) and that this could explain all rheumatic signs of SpA, including synovitis, which would be secondary to the release of proinflammatory mediators from the enthesis. This hypothesis was based on an MRI study in SpA and RA patients with recent-onset knee effusion, which showed that entheseal abnormalities were more prominent in SpA than in RA. Testing the validity of the proposed hypothesis is of relevance for both pathophysiological and clinical research since, if the hypothesis is correct, pathophysiological studies should focus on experimental models of enthesitis rather than synovitis, translational research should aim to obtain and study entheseal biopsies rather than synovial biopsies and clinical trials should focus on specific treatments targeting primary enthesitis rather than compounds directed towards secondary synovitis.

However, several remarks arise when critically assessing this hypothesis. First, the aforementioned MRI study suggests that enthesitis is more frequently seen during arthritis in established SpA than RA, but the cross-sectional design does not allow us to conclude that
enthesitis is primary to synovitis in SpA. Second, subsequent imaging studies comparing SpA with other inflammatory controls yielded conflicting results, questioning the specificity of enthesitis for SpA. Third, in patients with SpA-associated diseases without clinical arthritis, not only subclinical enthesitis, but also subclinical synovitis was shown to be present in a higher percentage compared with control patients. Fourth, the few studies examining the share of enthesitis and synovitis in sacroiliac joint biopsies and MRIs of the sacroiliac joints showed that synovitis and subchondral bone marrow changes (osteitis) were the most prominent features while enthesitis was neither the earliest nor the principal pathologic change.

Finally, animal models are not very useful in addressing this issue, as the ankylosing enthesitis model in DBA/1 mice clearly demonstrates that entheseal stress can lead to osteoproliferation and mild inflammation reminiscent of heel enthesitis in human SpA while, in contrast, both peripheral arthritis and axial spondylitis in human HLA-B27/β2 microglobulin transgenic rats are characterized by pronounced synovitis in the absence of enthesitis.

An additional issue with the enthesitis hypothesis is that this concept, which is based on imaging data, still lacks supportive information on the underlying cellular and molecular mechanisms. The few studies that have managed to obtain entheseal tissue samples from human SpA patients have yielded conflicting results on the major infiltrating cell types. Experimental studies suggested that TNF overexpression in the TNFΔARE model may drive enthesitis, but the same model shows extensive erosive polyarthritis phenocopying human RA rather than human SpA. Similarly, a ground-breaking mechanistic study recently provided convincing evidence that IL-23 overexpression induces enthesitis (including involvement of the aortic valve, an enthesis-like structure) by acting on double-negative, enthesis-resident T lymphocytes, but the same overexpression also leads to a severely destructive polyarthritis. Whereas these studies provide evidence that the TNF and IL-23/IL-17 cytokine axes may be involved in enthesitis in SpA, and thus that targeting these pathways may be an effective treatment strategy for this disabling SpA feature, they question at the same time the concept that SpA inflammation would primarily or uniquely target entheses. These experimental findings are consistent with the histological studies in established as well as early peripheral SpA demonstrating that the synovial inflammation is as pronounced but pathologically distinct from RA. Collectively these data challenge the concept that enthesitis is the primary lesion in SpA and rather suggest that different tissues of the skeleton (including the enthesis, the synovial membrane and the bone marrow) can be affected by TNF and IL-23/IL-17-mediated inflammation (Figure 1).

TOWARDS A UNIFYING CLINICAL CLASSIFICATION

Besides the discussed efforts to capture the different SpA manifestations into a unifying pathophysiological concept, increasing attempts have been made to define more clearly the clinical classification of SpA subtypes. SpA is classically subdivided into different phenotypic forms based on aetiology (reactive arthritis caused by a bacterial trigger), outcome (AS), associated extra-articular symptoms (PsA and IBD-related SpA) and a residual group called undifferentiated spondyloarthritis (USpA). Although this classification allows us to capture the clinical presentation in daily clinical practice reliably, it also presents a number of major
disadvantages. First, it does not reflect the increasing evidence that these phenotypes represent different presentations of a single disorder rather than a spectrum of distinct, though related, disease entities. The concept of SpA as a single disorder is not only based on the overlap between different subtypes in terms of genetic background, familial aggregation, immunopathology, and pathophysiology, but also on the clinical observation that a single patient can display several SpA phenotypes at once (e.g. a single patient can have AS plus PsA) or can evolve from one phenotype to another over time. For example, a substantial proportion of USpA patients with axial symptoms will evolve over time to full-blown AS, which relates to the fact that sacroiliitis on conventional radiographs, the hallmark of AS, can take years to develop. Second, the phenotypic subclassification favours clinical research in the major subtypes, AS and PsA, at the expense of less prevalent subtypes. For example, TNF blockers have been well studied and broadly implemented in AS and PsA but are still not registered for other SpA subforms. Finally, this phenotypic classification recognizes established, full-blown forms of SpA but fails to adequately capture less typical presentations of the disease.

In the early 1990s, two different classification criteria for SpA were developed: the Amor criteria and the European Spondyloarthopathy Study Group criteria. Recently the Assessment of SpondyloArthritis international Society (ASAS) developed novel classification criteria for SpA. Key aspects of these criteria are that (I) SpA is subdivided into axial SpA and peripheral SpA, (II) imaging abnormalities are not only defined by X-ray, but also by MRI, as new bone formation is a slow process that may take years to become visible on X-rays and (III) HLA-B27 positivity is an important entry criterion, allowing SpA patients without imaging abnormalities to be identified. The distinction between axial and peripheral disease in the ASAS

![Figure 1. Hypotheses on the development of arthritis in spondyloarthritis.](image)
criteria makes a lot of sense, as there is pathophysiological and therapeutic evidence that axial and peripheral disease may be driven by slightly distinct cellular and molecular mechanisms (e.g. the major cellular source of IL-17 in peripheral SpA is mast cells and to a lesser degree neutrophils, whereas neutrophils are the major IL-17-expressing cell population in axial SpA, and DMARDs might be effective in peripheral SpA, but not in axial SpA). Also, different outcome measurements are used for axial and peripheral disease. These novel criteria open new possibilities for clinical research, including therapeutic trials, in established as well as early SpA, as they are broader and more inclusive than the classical phenotypic classification.

**LIMITATIONS OF THE ASAS CLASSIFICATION CRITERIA**

Despite the aforementioned advantages of the new ASAS classification criteria, they also confront us with new challenges. First, these criteria were developed for classification, thereby to facilitate clinical research, but not for diagnosis. For example, a recent study compared the prevalence of axial SpA in at-risk patients with chronic back pain according to the ASAS axial SpA criteria with the diagnosis of axial SpA by the rheumatologist’s expert clinical diagnosis and concluded that the concordance yielded a kappa of only 0.41 (low to moderate agreement), suggesting that the ASAS axial SpA criteria and rheumatology experts captured somewhat different patient populations. According to the ASAS axial SpA criteria, 24% of the patients were undiagnosed and 21% were misdiagnosed in clinical practice, which could be interpreted as a false-positive diagnosis (in comparison with the gold standard, the rheumatologist’s expert opinion) in 24% of patients when applied as a diagnostic tool. This is probably related to the fact that MRI and HLA-B27 are major entry criteria in the ASAS classification but are diagnostically only useful in patients with a moderately high a priori chance of SpA.

A second limitation of the ASAS criteria is that the subdivision into either axial SpA or peripheral SpA is not a true reflection of the clinical reality since approximately 30% of the SpA patients have combined axial and peripheral disease manifestations. The ASAS proposed that the axial SpA criteria should be applied in patients with combined axial and peripheral disease. With this definition, however, there is a risk that a substantial number of SpA patients with peripheral disease and some degree of back pain will fail to be classified as axial SpA, and thus as SpA all together, despite fulfilling the peripheral SpA criteria. For example, an HLA-B27-negative patient with Crohn’s disease with a monoarthritis of the knee, active inflammatory back pain for 6 months, but normal imaging of the sacroiliac joints would not classify as SpA, since neither the imaging nor the HLA-B27 criterion are met, which are required for axial SpA. However, the patient would be classified as SpA if the peripheral SpA criteria had been used. This questions whether patients with active axial (back pain) as well as peripheral symptoms (arthritis, enthesitis or dactylitis) should not enter the ASAS criteria by either one of the two criteria arms (Figure 2).

A third challenge of the new criteria is that we need to reassess carefully specific subgroups of axial and/or peripheral SpA (e.g. HLA-B27-positive vs -negative patients, and patients fulfilling the imaging vs clinical arm of the axial SpA criteria) to see whether they are different in terms of disease activity, disease burden, long-term outcome and response to treatment. Many studies addressing the latter issue are being conducted and results are awaited.
Figure 2. Classification of patients with axial, peripheral or combined symptoms. Patients with pure active axial symptoms should be classified according to the axial SpA criteria, and patients with pure peripheral symptoms according to the peripheral SpA criteria. However, according to ASAS the patients with combined axial and peripheral symptoms could only classify as having SpA if they fulfill the axial SpA criteria. We propose a small modification to these criteria so patients with combined symptoms could enter either of the two criteria arms to reduce the chance that these patients unfairly misclassify as not having SpA.

**HOW TO MEASURE DISEASE ACTIVITY AND OUTCOME**

An additional issue arising here is that the heterogeneity of the disease manifestations of SpA not only make it a challenge to properly classify the disease, but also to measure the disease activity and outcome of therapy. Most disease activity and outcome parameters either capture only a single disease manifestation (axial, peripheral or extra-articular) or are only validated in a single phenotypic SpA subtype (AS or PsA). This hampers the evaluation of SpA as a whole, especially in patients with combined axial and peripheral disease manifestations, where well-validated AS parameters such as the BASDAI[63] and Ankylosing Spondylitis Disease Activity Score (ASDAS)[64,65] may underestimate peripheral disease activity and where swollen and tender joint counts as used in PsA miss aspects of axial disease. It remains to be determined whether global measurements such as patient’s and physician’s global assessments of disease activity are perhaps the most appropriate measurements to monitor disease activity in SpA patients with a combined phenotype.[62,66,67] Alternatively, it appears that measurements initially developed for axial disease, such as the BASDAI and ASDAS, may also be responsive to effective therapy in SpA patients with peripheral and/or combined disease.[62]

Besides the challenge to capture the different aspects of the disease in a single clinical disease activity measurement, an additional complication is that CRP and ESR are often normal in SpA. Therefore several groups have attempted to identify additional blood and/or target tissue biomarkers that reflect disease activity, such as MMP-3 in the blood[68] and CD163+ macrophages in the synovial tissue.[34] Unfortunately, these biomarkers are not sufficiently robust and reliable to be used as a surrogate marker in individual patients and thus their use remains restricted to
clinical trials. The same issue applies to biomarkers of structural damage in general and new bone formation in particular: measuring structural outcome by the gold standard of X-rays requires long-term observation and may be inadequate to assess new bone formation in peripheral disease, but biochemical biomarkers of structural outcome lack sensitivity and specificity. Collectively there is still a very high unmet need for reliable biomarkers to monitor disease activity (inflammation) and outcome (structural damage) in SpA.

OPTIMAL USE OF TNF BLOCKERS

One of the major drivers behind the current efforts to unify the SpA concept was the successful introduction of TNF blocking therapies in SpA 10 years ago. First, the major rationale for their use in SpA was the clinical and immunopathological overlap between SpA and Crohn’s disease. Second, the original trials were not restricted to a single subtype but included different forms of axial and peripheral SpA. And third, the subsequent phase III trials demonstrated clinical efficacy for axial disease, arthritis and enthesitis, as well as extraarticular manifestations such as uveitis, psoriasis and IBD. Collectively these data pointed towards TNF as an overarching inflammatory principle in SpA. Surprisingly, however, the clinical development programs of the previous decade were completely focused on AS and PsA and TNF blockers were neither studied nor registered in other SpA subforms. It has been only recently that the SpA community regained interest in exploring the potential use of TNF inhibitors in non-prototypical forms of SpA. Several clinical trials have shown that TNF blockers are not only effective in AS, but also in the non-radiographic forms of axial SpA. And several small studies have also reported that TNF inhibitors are equally efficacious in patients with non-AS, non-PsA peripheral SpA, which was recently confirmed in two randomized placebo-controlled clinical trials. Not only the clinical response, but also the immunopathological response in the synovial tissue upon effective treatment appeared to be similar across the different phenotypic subtypes in peripheral SpA. Taken together, these studies strongly support the notion that TNF inhibition should not be restricted to specific SpA subtypes but, on the contrary, should be made broadly available to treat the different disease manifestations in patients with diverse phenotypic presentations.

WHY DO WE NEED NEW THERAPIES?

TNF inhibitors have dramatically improved the treatment and care of SpA patients, but there is still a high unmet need for other and better therapeutic compounds. First, up to 40% of patients do not respond well to anti-TNF treatment, either due to adverse reactions and intolerance or due to inefficacy. One of the proposed mechanisms behind the inefficacy of TNF blockers is the development of anti-drug antibodies that can either increase the clearance of the TNF inhibitor or directly neutralize the functional part of the biologic drug. Whether this is also a real clinical issue in the treatment of SpA is still to be determined. If immunogenicity is a real issue, it could be useful to try a second or third TNF inhibitor, but registry studies indicate that the response rate and drug survival decrease with each TNF inhibitor.
Second, TNF blockade does not induce long-lasting remission. In axial SpA, almost all patients relapse after interruption of treatment, often after a couple of months. Moreover, recently we also found similar relapse rates in peripheral SpA.302

Third, TNF blockade halts joint destruction104 but fails to slow down new bone formation. The lack of effect on osteoproliferation has been previously reported for axial disease in AS105-107 and more recently also for peripheral disease in PsA.71 It remains highly debated whether osteoproliferation might be halted if anti-TNF treatment is started earlier in the disease course108 or whether bone remodelling is really independent from inflammation and has to be targeted separately.109 Although there is emerging evidence that high-dose NSAIDs may have an inhibitory effect on new bone formation,110-113 developing adequate treatments to halt new bone formation is still a major unmet medical need in SpA as, e.g. physical function is independently determined by both disease activity and radiographic damage of the spine.114 Taken together, the lack of efficacy and/or intolerance in a significant proportion of patients, the rapid relapse upon treatment interruption and the failure to halt new bone formation emphasize the need for other effective treatments besides TNF blockade in SpA.

WHICH EXISTING COMPOUNDS HAVE BEEN TESTED SO FAR?

Several compounds have been tested in SpA (mainly AS and PsA) based on their efficacy in diseases such as RA and psoriasis, but none of these compounds has proven to be highly effective (Table 1). First, T cell- and B cell-targeted therapies such as abatacept (CTLA4-Ig),115-117 alefacect (anti-LFA3),118-119 efalizumab (anti-CD11a)120 and rituximab (anti-CD20)121-125 only showed modest, if any, therapeutic efficacy in SpA, which is consistent with the concept that SpA belongs to the class of autoinflammatory rather than autoimmune disorders.126 Second, biologic therapies targeting key proinflammatory cytokines other than TNF have not been successful, as blockade of IL-1 with anakinra127-129 and inhibition of IL-6 with both tocilizumab130 and sarilumab131 failed to show clinical efficacy in AS. Third, other small molecule compounds such as thalidomide132,133 and pamidronate (a bisphosphonate)134 also failed, as these drugs were respectively too toxic for widespread use and only moderately effective in AS.

NOVEL TREATMENT OPTIONS ON THE HORIZON

In contrast to the previously mentioned treatments, a number of novel treatment strategies have recently yielded promising results in SpA (Table 1). Apremilast, an orally available small molecule inhibitor of phosphodiesterase 4 (PDE4), which increases intracellular cyclic adenosine monophosphate (cAMP) and thus modulates multiple pro- and anti-inflammatory mediators, has demonstrated clinical efficacy in PsA135 and a possible trend towards clinical effect in AS136 in phase II trials. The major interest, however, has recently focused on therapies targeting the IL-23/IL-17 axis, as there is an extensive rationale for targeting this pathway in SpA. First, AS as well as the SpA-associated disorders psoriasis and Crohn’s disease are associated with a single nucleotide polymorphism of IL-23R.137-139 Second, in vitro evidence indicates that the unfolded protein response, a cellular stress programme that can be initiated by HLA-B27 misfolding,
### Tabel 1. Summary of clinical trials in SpA with compounds other than NSAIDs, DMARDs or TNF inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Study design</th>
<th>SpA subtype</th>
</tr>
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<tbody>
<tr>
<td><strong>T-cell and B-cell targeted biological therapies</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Abatacept</td>
<td>Inhibits T-cell co-stimulation</td>
<td>Randomized, double-blind, placebo-controlled, phase II trial</td>
<td>PsA</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Inhibits T-cell co-stimulation</td>
<td>Open-label study</td>
<td>AS</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Inhibits T-cell co-stimulation</td>
<td>Open-label study</td>
<td>Axial SpA</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Inhibits T-cell activation</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>PsA</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Inhibits T-cell activation</td>
<td>Open label extension study</td>
<td>PsA</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Inhibits T-cell activation</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>PsA</td>
</tr>
<tr>
<td>Rituximab</td>
<td>B-cell depletion</td>
<td>Open-label study</td>
<td>AS</td>
</tr>
<tr>
<td><strong>Anticytokine biological therapies</strong></td>
<td></td>
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<tr>
<td>Anakinra</td>
<td>IL-1R inhibitor</td>
<td>Open-label study</td>
<td>AS</td>
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<td>Anakinra</td>
<td>IL-1R inhibitor</td>
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<td>PsA</td>
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<td>Tocilizumab</td>
<td>IL-6R inhibitor</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>AS</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>IL-6R inhibitor</td>
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<td><strong>Secukinumab</strong></td>
<td>IL-17A inhibitor</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>AS</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>IL-17A inhibitor</td>
<td>Randomized, double blind, placebo-controlled, phase II trial</td>
<td>PsA</td>
</tr>
<tr>
<td><strong>Ustekinumab</strong></td>
<td>IL-23 and IL-12 inhibitor</td>
<td>Randomized, double blind, placebo-controlled, cross-over, phase II trial</td>
<td>PsA</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-23 and IL-12 inhibitor</td>
<td>Randomized, double blind, placebo-controlled, phase III trial</td>
<td>PsA</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-23 and IL-12 inhibitor</td>
<td>Randomized, double blind, placebo-controlled, phase III trial</td>
<td>PsA</td>
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<tr>
<td>Treatment arms</td>
<td>Primary outcome</td>
<td>Main results</td>
<td>Reference</td>
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<tr>
<td>----------------</td>
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<tr>
<td>Abatacept 10 mg/kg (n=40)</td>
<td>ACR20 at day 169</td>
<td>Placebo: 19% 3 mg/kg: 33% 10 mg/kg: 48% 30/10 mg/kg: 42%</td>
<td>[115]</td>
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<tr>
<td>Anti-TNF naive (n=15)</td>
<td>ASAS40 at week 24</td>
<td>Anti-TNF naive: 13% Anti-TNF IR: 0%</td>
<td>[116]</td>
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<tr>
<td>Abatacept 10 mg/kg (n=7)</td>
<td>BASDAI50 at week 24</td>
<td>14%</td>
<td>[117]</td>
</tr>
<tr>
<td>Placebo + MTX (n=62)</td>
<td>ACR20 at week 24</td>
<td>Placebo + MTX: 23%</td>
<td>[118]</td>
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<tr>
<td>Alefacept + MTX (n=160)</td>
<td>ACR20 at week 24</td>
<td>54%</td>
<td>[119]</td>
</tr>
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<td>Placebo (n=53)</td>
<td>ASAS20 at week 24</td>
<td>Placebo: 28%</td>
<td>[120]</td>
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<td>Anti-TNF naive (n=10)</td>
<td>ASAS20 at week 24</td>
<td>Anti-TNF naive: 30% Anti-TNF IR: 50%</td>
<td>[121]</td>
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<td>Rituximab day 0 and 14 (n=9)</td>
<td>PsARC at week 24</td>
<td>56%</td>
<td>[123]</td>
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<tr>
<td>Rituximab day 0 and 15 (n=20)</td>
<td>ACR20 at week 24</td>
<td>35%</td>
<td>[124]</td>
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<tr>
<td>Anakinra 100 mg/day (n=9)</td>
<td>ASAS20 at 3 months</td>
<td>67%</td>
<td>[127]</td>
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<td>Anakinra 100 mg/day (n=20)</td>
<td>ASAS20 at week 24</td>
<td>25%</td>
<td>[128]</td>
</tr>
<tr>
<td>Anakinra 100 mg/day (n=20)</td>
<td>PsARC at week 24</td>
<td>30%</td>
<td>[129]</td>
</tr>
<tr>
<td>Placebo (n=51)</td>
<td>ASAS20 at week 12</td>
<td>Placebo: 28% Tocilizumab: 37%</td>
<td>[130]</td>
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<tr>
<td>Sarilumab 100 mg/week (n=52)</td>
<td>Sarilumab 100 mg/week: 19% Sarilumab 150 mg/week: 38% Sarilumab 100 mg/2 weeks: 19% Sarilumab 150 mg/2 weeks: 30% Sarilumab 200 mg/2 weeks: 30%</td>
<td>[126]</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=50)</td>
<td>ASAS20 at week 12</td>
<td>Placebo: 24%</td>
<td>[131]</td>
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<tr>
<td>Placebo (n=6)</td>
<td>ASAS20 at week 6</td>
<td>Placebo: 17% Secukinumab: 61%</td>
<td>[146]</td>
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<tr>
<td>Ustekinumab till week 12 (n=76)</td>
<td>ACR20 at week 12</td>
<td>Placebo: 14% Ustekinumab: 42%</td>
<td>[148]</td>
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<tr>
<td>Placebo (n=206)</td>
<td>ACR20 at week 24</td>
<td>Placebo: 23% Ustekinumab 45 mg: 42% Ustekinumab 90 mg: 50%</td>
<td>[149]</td>
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<tr>
<td>Placebo (n=104)</td>
<td>ACR20 at week 24</td>
<td>Placebo: 20% Ustekinumab 45 mg: 44% Ustekinumab 90 mg: 44%</td>
<td>[150]</td>
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strongly increases the production of IL-23, and macrophages of AS patients tend to produce increased amounts of IL-23. Third, the number of circulating CD4+ IL-17 T cells is increased in AS, especially the KIR3DL2-expressing T cells that respond to cell surface HLA-B27 homodimers and IL-17-producing γδ T cells. Fourth, we and others have demonstrated increased IL-17 expression by innate immune cells such as neutrophils and mast cells in SpA target tissues such as the facet joints and synovial tissue. Finally, IL-23 overexpression in mice was recently shown to induce enthesitis, which may partially phenocopy human SpA via ROR-γt+ CD3+ CD4- CD8- T cells, which elaborate proinflammatory cytokines including IL-17 and IL-22.

More importantly, however, a proof-of-concept randomized placebo-controlled trial with secukinumab, a fully human anti-IL-17A monoclonal antibody, in AS demonstrated high response rates, with >60% of the patients reaching a 20% improvement in ASAS criteria (ASAS20) as early as week 6 of treatment. A similar trial with secukinumab showed a trend towards clinical efficacy in PsA, whereas ustekinumab, a monoclonal antibody directed against the p40 chain common to both IL-23 and IL-12, was superior to placebo in several clinical trials in PsA. Ongoing clinical trials will have to determine the exact efficacy and safety of several compounds targeting the IL-23/IL-17 axis for treatment of the different disease manifestations of SpA, including the potential effect on structural damage. Such compounds may not only be directed towards key cytokines of this axis, but may also directly target a specific pathogenic IL-17-producing cell population. For example, a small open-label trial has shown some positive clinical effects of treatment with imatinib, a tyrosine kinase inhibitor that may target c-kit-positive mast cells and innate lymphoid cells as potential sources of IL-17 in SpA. Similarly, small molecules targeting key transcription factors of the IL-17 axis, such as RORγ, are currently in preclinical development and may be further explored for the treatment of SpA.
CONCLUSION

The global management of SpA has dramatically improved over the last 15 years, not only by the introduction of TNF blockers for this disease, but also by ongoing efforts to develop unifying concepts and to understand pathogenic pathways underlying the different phenotypic SpA manifestations. Further progress is expected from studies focusing on early disease recognition, proper classification and adequate assessment and monitoring of disease activity of not only AS and PsA, but also other SpA forms. This needs to be combined with clinical trials focusing on the optimization of existing therapies, such as TNF blockade for early and/or atypical disease, as well as clinical development of novel drugs, in particular those targeting the IL-23/IL-17 pathways. The aim is not only to discover novel anti-inflammatory alternatives for TNF inhibition in SpA, but to develop genuine disease-modifying and remission-inducing therapies. Moreover, the ongoing proof-of-concept studies with novel targeted therapies will also provide further clues regarding the pathophysiologic mechanisms behind the different disease manifestations of SpA and are thereby likely to contribute to the development of unifying translational concepts for this disabling disorder.

RHEUMATOLOGY KEY MESSAGES

- SpA is a disease with heterogeneous manifestations that share a common pathophysiologic background.
- Promising novel therapeutic options for SpA, such as those targeting the IL-23/IL-17 axis, are pending.
- Future compounds have to be tested in SpA as a whole, regardless of subphenotype.
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