




REVIEW

Recent advances in ankylosing spondylitis: understanding the disease and management [version 1; referees: 2 approved]

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Abstract

The term spondyloarthritis refers to a group of immune-mediated diseases characterised by inflammation of the axial skeleton, peripheral joints, and entheses. Ankylosing spondylitis (AS) is the most common and characteristic of these entities and even though it was first described over two centuries ago, the understanding of the underlying disease mechanism remains incomplete. It is known that around 40% of patients with AS have subclinical bowel inflammation, suggesting that the origin of the disease could be in the gut. Also, more genes and new molecules have demonstrated a role in the pathogenesis of AS. In this review, we analyse the latest therapies for spondyloarthritis and the most relevant discoveries over the last three years, together with their implications for different aspects of the disease.

Keywords

Ankylosing spondylitis, spondyloarthritis, spondyloarthropathy, management, pathogenesis

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Introduction

Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory arthritis included in the so-called group of spondyloarthritis (SpA). It typically develops in males in their third decade of life and affects mainly the axial skeleton and the sacroiliac joints. Although the oldest descriptions date from the time of Galen, it was not until the 19th century that the disease could be accurately diagnosed on the basis of reports by Vladimir Bekhterev, Adolph Strümpell, and Pierre Marie. The HLA-B27 allele is known to have a strong association with the disease¹; however, other genes play a part in its development. The discovery of several inflammatory pathways led to the era of the biologic therapies, which meant a revolution in the treatment and prognosis of AS. Tumour necrosis factor inhibitors (TNFis) were the first ones to be approved, but in the last few years the interleukin-17 (IL-17)/IL-23 axis has gained relevance, culminating in the licence of new biological disease-modifying antirheumatic drugs (bDMARDs) blocking IL-17.

In spite of all of these advances, the disease mechanisms underlying the disease are not fully understood and new information concerning the pathogenesis, triggers, and the outcome of new treatments continues to appear. In this review, we will focus on the advances of the last three years regarding the above aspects of AS.

Genetics

AS is considered an inherited disease, as over 90% of the risk for its development relies on genes². However, the HLA-B27 allele accounts for only 20% of the genetic effect¹. Other alleles, especially HLA-B, are thought to play an important role in the disease: HLA-B*13:02, HLA-B*40:01, HLA-B*47, and HLA-B*51 are some examples³. The most significant discovery of the last three years has been the interaction of ERAP1, the protein endoplasmic reticulum aminopeptidase 1, with the HLA-B alleles, resulting in a higher risk of developing AS. The main variant of the gene (rs30187, K528R) interacts only with the HLA-B27 allele, and in patients who are HLA-B27 negative, ERAP1 interacts with the HLA-B40 allele⁴. The mechanism underlying the increased risk remains unclear; nevertheless, it is known that the presence of this gene is not related to the radiographic severity of the disease⁵.

A recent study reported that a lower copy number of the *TLR7* gene was a marker for susceptibility to AS in males but behaves as a protective factor in women⁶. Ruan *et al.*⁷ found that genetic polymorphisms of IL-12B (rs6871626) and IL-6R (rs4129267) were associated with an increased risk of AS independently of gender and also could function as biomarkers for diagnosis and prognosis.

Genome-wide association studies have shown that the T helper 17/23 (Th17/23) axis and its multiple genetic polymorphisms are involved not only in AS but also in inflammatory bowel disease (IBD) and psoriasis, supporting the hypothesis that there is a common underlying pathogenic mechanism and that the microbiome seems to be implicated in the development of the diseases⁸.

Pathogenesis

How HLA-B27 initiates AS is unknown, and, after many years, some of the earliest hypotheses are still being investigated. The original hypothesis, called the ‘arthritogenic peptide theory’, suggests that the presentation of either bacterial peptides by HLA-B27 or self-mimicking HLA-B27-binding peptides from certain bacteria could initiate a cell-mediated immune reaction leading to AS⁹. The second one is the ‘unfolded protein response’ hypothesis, which suggests that HLA-B27 tends to misfold and accumulate in the endoplasmic reticulum, triggering a stress response that results in the release of IL-23^{10,11}. However, a new study¹² has questioned these two theories, claiming that the arthritogenic peptide theory should be reassessed in terms of quantitative changes concerning self-peptide presentation and T-cell selection. It also stated that the absolute binding preferences of HLA-B27 allotypes are not sufficient to explain the association of the disease.

The third hypothesis is the ‘HLA-B27 homodimer model’¹³, which supports the view that HLA-B27 homodimers have an abnormal interaction with natural killer (NK) and CD4 T cells. Unlike the heterodimeric form of HLA-B27, the homodimer is able to bind to certain killer cell immunoglobulin-like receptors (KIRs), which are expressed on NK cells and T cells, causing the release of IL-17^{14–16}. Ridley *et al.*¹⁷ have proven that CD41 T cells upregulate the expression of KIR-3DL2 on the cell surface and that the binding of this receptor to HLA-B27 potentiates T-cell survival and Th17 cell differentiation. Th17 cells are a type of T-helper lymphocyte which produces IL-17¹⁸, a cytokine able to increase T-cell priming and stimulate immune cells such as fibroblasts and macrophages promoting the release of IL-6, TNF- α , and other chemokines¹⁹.

Oppmann *et al.* found that IL-23 is one of the triggers of the Th17 response²⁰. This molecule is a pro-inflammatory cytokine that seems to play an important part in stabilising Th17 cell phenotype through the transcription factor Blimp-1 (Prdm1)²¹, which is associated with Crohn’s disease²². Th17 cells are commonly found in the intestinal lamina propria of the gut²³ and their instability can be induced by exposure to certain bacteria, leading to the transition of Th17 cells into regulatory T (Treg) cells²⁴. Maxwell *et al.*²⁵ also suggested that IL-23 promotes the accumulation of Treg cells in the bowel, some of which probably were Th17 previously^{26,27}.

Microbiome

Gut mucosal inflammation is estimated to be present in 70% of patients with AS²⁸, progressing to clinical IBD in 5% of cases. Crohn’s disease and ulcerative colitis are characterised by having gut dysbiosis (a qualitative or quantitative microbial imbalance) which is also seen in AS²⁹. The Ghent inflammatory arthritis and spondylitis cohort (GIANT) studies strongly support the concept that there is a relationship between gut inflammation and the pathogenesis of AS^{30–32}. One of the theories to explain it is that a constant antigenic stimulation can activate T cells and this might be responsible for chronic bowel inflammation³³. Other studies suggest that patients with AS (and their first-degree relatives) have a high gut permeability,

which increases their exposure to gut microbes³⁴. In addition, animal studies proved that HLA-B27 alone was insufficient to develop AS, since transgenic rats that had been raised in a germ-free environment did not develop features of SpA³⁵. In the last few years, investigators have focussed on detecting pathogens as triggers for AS. *Klebsiella pneumoniae* was the first to be reported³⁶: this bacterium is thought to carry an antigen that resembles a molecule coded by the *HLA-B27* gene; however, the mechanism is not fully understood and other studies have stated that its involvement in AS is unlikely. Other relevant families of bacteria that have been associated with the development of AS are *Lachnospiraceae*, *Prevotellaceae*, *Rikenellaceae*, *Porphyromonadaceae*, and *Bacteroidaceae*. Non-gut bacteria are also thought to be involved: periodontal disease has become a possible target as anti-*Porphyromonas gingivalis* and anti-*Prevotella intermedia* antibodies are detected in high titres in patients with SpA³⁷. Some studies even suggest that chronic periodontitis is associated with severe spinal dysmobility in AS³⁸. Nevertheless, it is still an area of investigation, as recently published results contradict these findings³⁹.

Gender differences

Evidence gained in the last few years suggests that AS affects men and women differently. Landi *et al.*⁴⁰ analysed a sample of 2,044 patients with AS and reported that disease commences earlier in men but that the diagnosis is usually more delayed than in women. Men have lower disease activity measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Assessment of SpondyloArthritis international Society (ASAS)-endorsed Disease Activity Score (ASDAS) and a better quality of life (Ankylosing Spondylitis Quality of Life Questionnaire, or ASQoL) but have worse spinal mobility (Bath Ankylosing Spondylitis Metrology Index, or BASMI) and a more serious radiologic progression (Bath Ankylosing Spondylitis

Radiology Index, or BASRI). In contrast, women usually have more peripheral arthritis and an increased prevalence of arthritis, dactylitis, and enthesitis combined with a worse quality of life and a worse response to anti-TNF treatment⁴¹. This contradicts the results reported by Webers *et al.*⁴², who agreed that men had more radiographic damage and a better quality of life but did not find differences in disease activity or physical function. However, the authors analysed only 216 patients.

Therapies

Since 2015, there has been remarkable progress concerning the therapeutic management of AS. New treatments and strategies have paralleled the description of new pathogenic mechanisms. Table 1 summarises the most relevant drugs and their mechanism of action; some are still under investigation^{43–55}.

Tumour necrosis factor inhibitors

The first bDMARDs were approved several years ago. As the patents of some of these drugs were closer to expiration, pharmaceutical companies focused their interest on developing more affordable drugs. CT-P13, the infliximab biosimilar, was the first one to be released⁴³, followed by Benepali (SB4), the etanercept biosimilar, in 2016⁵⁶. Multiple trials endorse the similar safety and efficacy of CP-P13 and infliximab not only in patients with AS but also in the treatment of rheumatoid arthritis (RA). The PLANETAS study reported comparable results for patients with AS regarding ASAS20 and ASAS40⁵⁷. The extension of the study showed that switching from infliximab to its biosimilar did not imply negative effects on safety or efficacy⁵⁸. These findings were also confirmed in the PLANETRA study, carried out in patients with RA^{59,60}. In regard to Benepali (SB4), the most important efficacy and safety studies have been carried out in RA, showing results similar to those obtained with Enbrel⁴⁴. As far as therapy switching is concerned, the

Table 1. Novel approaches for the management of ankylosing spondylitis.

Therapy	Reference	Mechanism of action	Current status
CT-P13 (infliximab biosimilar)	43	Anti-TNF	Approved for use in AS
SB4 (etanercept biosimilar)	44	Anti-TNF	Approved for use in AS
Secukinumab	45	Anti-IL-17A	Approved for use in AS
Ixekizumab	46	Anti-IL-17A	Under investigation. Primary endpoints met.
Brodalumab	47	Anti-IL-17R	Not approved owing to safety issues
Ustekinumab	48,49	Anti-IL-12/IL-23	Not approved owing to lack of efficacy
ABT-122	50	Anti-IL-17A/TNF- α	Under investigation. Successful phase II clinical trials
COVA322	51	Anti-IL-17A/TNF- α	Not approved owing to safety issues
CBP30	52	CBP/p300 bromodomain inhibition	Future trials announced
Sarilumab	53	Anti-IL-6R α	Not approved owing to lack of efficacy
Tofacitinib	54	JAK inhibitor	Under investigation. Successful phase II clinical trials

AS, ankylosing spondylitis; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor.

safety and efficacy are maintained after switching from Enbrel to Benepali in patients with RA⁶¹, and a study is taking place in Germany to assess this transition in patients with AS⁶².

Interleukin inhibitors

The approval of secukinumab, a fully human monoclonal antibody able to neutralise IL-17A, has been a major advance in the treatment of AS⁴⁵. Patients with AS are known to have high levels of this interleukin⁶³, which is critically involved in the pathogenesis of the disease. IL-23 is secreted by antigen-presenting cells and stimulates Th17 cells, which are defined by their production of IL-17 cytokines⁶⁴.

Two double-blind, placebo-controlled, phase III clinical trials—MEASURE 1⁶⁵ and MEASURE 2⁶⁶—reported a significant improvement in disease activity in patients with AS with effects sustained over 2 years; this was combined with a good safety profile. Pavelka *et al.*⁶⁷ recently published the results of MEASURE 3, a randomised, double-blind, phase III trial in patients with active AS. In accordance with previous studies, a significant improvement was reported in the 16-week follow-up compared with placebo and this was sustained until week 52. The patients initially on placebo, who were randomly assigned on week 16, also experienced improvement through week 52. During this time, no major new adverse events were noted. In addition, MEASURE 5, another randomised, double-blind, phase III trial is ongoing. It is also comparing the safety and tolerability of secukinumab in patients with active AS versus placebo⁶⁸.

Nevertheless, there are other drugs targeting IL-17. COAST-W⁶⁹ is a phase III, randomised, double-blind, placebo-controlled trial assessing the effect of ixekizumab on radiographic axial SpA. Ixekizumab is also a fully human monoclonal antibody that binds to IL-17A. The first results show that the drug met all of the primary and secondary endpoints. Brodalumab, a monoclonal antibody neutralising IL-17R, proved its efficacy for psoriatic arthritis; however, development was paused after a higher incidence of suicidal ideation was noted⁴⁷.

IL-23 is directly related to the development of enthesitis⁷⁰, and the IL-23/IL-17 axis occupies a central place in the pathogenesis of SpA. Ustekinumab is a human monoclonal antibody targeting the p40 subunit of IL-12 and IL-23. It is considered one of the most effective treatments for psoriasis⁷¹; however, its efficacy in AS has not been as expected, and results have been contradictory: TOPAS, a prospective, open-label, single-arm, proof-of-concept clinical trial⁷², reported a reduction of signs and symptoms in patients with active AS. In contrast, a phase III, multicentre, randomised, double-blind, placebo-controlled study⁴⁸ evaluating the efficacy and safety of ustekinumab in the treatment of non-radiographic axial SpA had to end prematurely after a related study⁴⁹ did not achieve the key points.

In regard to future approaches, ABT-122, an immunoglobulin molecule targeting both IL-17A and TNF- α , has recently demonstrated its efficacy in phase I and II trials for RA and psoriatic arthritis^{50,73}; however, given the importance of IL-17 in the pathogenesis of AS, it is expected that trials in patients

with AS will commence soon. COVA322⁷⁴ is another dual agent, a fusion protein antibody able to bind TNF- α and IL-17A. It was thought to be a promising therapy for AS; however, owing to safety issues in a trial for psoriatic arthritis, investigations have not gone further⁵¹. CBP30⁵² is a selective inhibitor of CBP/p300 bromodomains able to suppress the production of cytokines by Th17 cells in patients with AS and healthy controls. Future trials with this molecule have been announced. Sarilumab, a fully human monoclonal antibody that blocks the α -receptor of IL-6, demonstrated a lack of efficacy for the treatment of AS in the ALIGN study⁵³.

Janus kinase inhibitors

Tofacitinib, a Janus kinase (JAK) inhibitor, is also able to interfere in the inflammatory cascade of IL-17, IL-21, and IL-23. In a 16-week clinical trial (with 12 weeks of treatment and 4 weeks of washout period), van der Heijde *et al.* reported the superiority of the 5 mg dose twice a day versus placebo: 63% and 40% of patients, respectively, achieved ASAS20 after 12 weeks⁵⁴.

An important aspect for biologic therapies is the cost. As more patients receive bDMARDs, healthcare systems have been forced to find new ways to cope financially: one cost-saving strategy is tapering. The 2016 update of ASAS-European League Against Rheumatism (ASAS-EULAR) recommendations for the management of axial AS⁷⁵ suggested that patients in sustained remission are candidates to taper the dose of the drug. However, there is controversy regarding this approach because of conflicting results. One single-centre prospective study⁷⁶ compared the evolution of two groups of patients: one receiving TNFis at the standard dose and another group with down-titration. After one year of treatment, the clinical outcomes were similar in the two arms but costs were significantly reduced in the latter group. Plasencia *et al.*⁷⁷ previously reported similar results in a retrospective study comparing patients in Spain on tapering strategy versus patients on standard dose from the Netherlands. Even though the proportion of patients who maintained remission was similar, those in the tapering group had more flares than the patients receiving the standard dose. Regarding radiographic progression, Park *et al.*⁷⁸ found that patients who had syndesmophytes at baseline had a more rapid radiographic progression if they received a tapering regime.

Other therapies

bDMARDs are not the only therapies that have been developed within the last few years. Fattahi *et al.*⁷⁹ reported the results of a randomised, placebo-controlled trial of a new non-steroidal anti-inflammatory drug (NSAID): B-D-mannuronic acid. The 12-week ASAS response was similar to that obtained with naproxen, and the safety profile was considerably better; there were no renal side effects and gastrointestinal tolerability was good.

There has also been controversy regarding the administration of NSAIDs. Wanders *et al.*⁸⁰ reported that continuous administration of NSAIDs reduced radiographic progression in comparison with on-demand therapy, whereas more recently Sieper *et al.*⁸¹ found that continuous treatment with diclofenac

for 2 years did not reduce radiographic progression compared with an on-demand administration.

Biomarkers

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are two acute-phase reactants that classically have been used to assess the presence of inflammation in patients. Unfortunately, they are not specific and the sensitivity is also low⁸², especially in patients with non-radiographic axial SpA⁸³ where acute-phase proteins remain within normal limits most of the time.

Owing to the lack of a reliable test, many studies have tried to find a biologic marker capable of predicting a clinical outcome or disease activity in AS. After the discovery of new pathological pathways, interleukins became targets. IL-6 was in the spotlight for some years; but, whereas some studies reported an association between IL-6 and disease activity^{84–86}, others produced opposite results^{87,88}.

Calprotectin is a dimer of calcium-binding proteins used as a surrogate marker for gut inflammation. Its main application is monitoring disease activity in IBD⁸⁹. Both Crohn's disease and ulcerative colitis are known to be associated with AS. The pathway is not clear; there are discrepancies concerning whether gut inflammation is the cause or the consequence of musculoskeletal disease. Given this, studies have tried to evaluate calprotectin for the management of AS. Duran *et al.*⁹⁰ found that faecal calprotectin was associated with a higher disease activity and is a better predictor of bowel involvement than CRP, ESR, BASDAI, and Bath Ankylosing Spondylitis Functional Index (BASFI). Klingberg *et al.*⁹¹ confirmed these results and also suggested that calprotectin could be used to identify patients with AS at high risk of developing IBD. In accordance with this, another study⁹² demonstrated that exercise could decrease the levels of calprotectin in patients with AS and that this was associated with a reduction of disease activity.

Bone involvement

A typical feature of AS is bone formation co-existing with bone resorption. As with many other inflammatory diseases, there is an imbalance between these processes, which results in the appearance of syndesmophytes and bone erosions in patients with AS⁹³. IL-17, one of the most active cytokines in SpA, has a major role promoting osteoclastogenesis directly and through the activation of receptor activator of nuclear factor kappa B (RANK)^{94,95}. However, it does not exert its action alone; it works in combination with TNF- α . The latter molecule triggers bone destruction through the RANK-RANK ligand (RANK-RANKL) system and inhibits bone formation via the overexpression of Dickkopf-related protein 1 (DKK1)⁹⁶, which suppresses the WNT bone pathway^{96,97}. WNT/b-catenin signalling is a regulator of osteogenesis and its high levels promote the formation of osteoblasts and reduce osteoclastogenesis (and therefore bone resorption)⁹⁸. In contrast to TNF- α , IL-17 has a dual effect because it can promote not only bone destruction by acting complementarily with TNF- α ⁹⁹ but also bone formation at sites of inflammation or exposed to mechanical stress¹⁰⁰. An international

study¹⁰¹ reported contradictory results, as they found that patients with AS had decreased indicators of osteoclast formation and bone resorption, suggesting a reduced capacity of osteoclast precursors to differentiate into osteoclasts and resorb, probably because of low RANKL/OPG and CD51/CD61 expression.

Ranganathan *et al.*¹⁰² found that macrophage migration inhibitory factor (MIF) was able to act on osteoblasts, promoting inflammation and new bone formation. They also suggested that the main source of MIF-producing cells was in the gut and that certain pathogens can induce its release. In addition, the level of MIF was predictive of progressive spinal damage.

More cytokines are being implicated in the pathogenesis of AS. El-Zayadi *et al.*¹⁰³ recently reported that IL-22 regulates the function of mesenchymal cells, inducing proliferation, migration, and osteogenesis, in an inflammation-dependent context. IL-32 γ has been shown to be elevated in the joints and tissues of patients with AS and is able to induce osteoblast differentiation and atypical new bone formation¹⁰⁴. Another interleukin, IL-37, is also elevated in patients with osteoporosis in addition to AS, and its levels correlate with disease activity and bone mineral density¹⁰⁵. This is consistent with Kwon *et al.*¹⁰⁶, who found that osteoblast-lineage cells are increased in patients with AS and are reduced after therapy with infliximab. They also reported that the drug allows mature osteoblast differentiation in late inflammation.

Machado *et al.*¹⁰⁷ stated that fat deposition in the vertebral corners is associated with radiographic progression, and they postulated that there should be a 'window of opportunity', as fat lesions can be preceded by inflammatory lesions. Interestingly, they also found that even though the absence of bone marrow oedema and fat deposition was negatively associated with radiographic progression, there was still bone formation in those areas, implying that there must be other pathways stimulating osteoproliferation.

Imaging

The assessment of structural damage is valuable in patients with AS. The modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (which consists of the sum of scores of the lumbar and cervical spine from a lateral view, ranging from 0 to 72) is a commonly used method for detecting changes in plain radiographs¹⁰⁸; however, X-rays are not a very sensitive tool and they are not able to properly differentiate squaring of vertebral bodies. Kim *et al.*¹⁰⁹ evaluated the squaring of the first sacral vertebra (S1) by using a method proposed by Ralston *et al.*¹¹⁰: squaring was associated with mSASSS and changes in magnetic resonance imaging (MRI) and therefore suggested that this assessment could be used to predict early axial involvement of the spine in AS. Regarding other predictors of progression, Dougados *et al.*⁵⁵ found that HLA-B27-negative patients with normal CRP and normal MRI of the sacroiliac joints have a 1.2% likelihood of progressing to radiological axial SpA within 5 years. This likelihood of progression increased to 18.4% in HLA-B27-positive patients, with raised CRP and

bone marrow oedema in the MRI of the sacroiliac joints. In HLA-B27-positive patients, smoking also seems to be associated with a proliferative metabolic pattern of the cartilage, which could justify its outgrowth and the development of enthesopathic lesions¹¹¹.

Althoff *et al.* were the first to suggest that contrast was not needed to assess axial activity in AS¹¹². However, Zhao *et al.*¹¹³ confirmed these results by using a large sample of patients, showing that the combination of short tau inversion recovery (STIR) and diffusion weighted imaging (DWI) in MRI is sufficient to monitor disease activity, avoiding the unnecessary use of contrast with its risks. Conversely, Bradbury *et al.*¹¹⁴ found that DWI has a moderate utility for assessing disease activity or monitoring response to treatment; however, it seems to be a great tool to distinguish axial SpA and non-inflammatory back pain.

Another MRI finding has been the discovery of the ‘backfill sign’. It was initially described by Weber *et al.*¹¹⁵, who defined it as a high signal intensity filling the sacroiliac joint space on T1-weighted images which could represent fat metaplastic tissue filling excavations in subchondral bone; however, the

histopathological origin has not been assessed yet. Recently, studies confirmed that the ‘backfill sign’ had a high specificity for SpA (between 95.8% and 98%)¹¹⁶ but the sensitivity was only 59%¹¹⁷. Therefore, its presence could be used to support the diagnosis of axial SpA, but its absence should not be used to exclude it.

Summary

The numerous investigations and studies carried out within the last three years have improved the understanding of the pathogenesis of AS. This has facilitated the development of new treatment strategies with the consequent improvement of the quality life of patients with SpA. As more is known about the disease, the greater the complexity that is revealed, emphasising the need to continue investigation to achieve even more efficient control of the disease.

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The referees who approved this article are:

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