Advances in managing ankylosing spondylitis

David I. Daikh[1,2]* and Patty P. Chen[1]

Addresses: [1]Division of Rheumatology, University of California, San Francisco, 400 Parnassus Avenue, San Francisco, CA 94143, USA; [2]San Francisco VA Medical Center, 4150 Clement Street, San Francisco, CA 94121, USA

* Corresponding author: David I. Daikh (david.daikh@ucsf.edu)

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Abstract

Ankylosing spondylitis (AS) is a chronic inflammatory disease with prominent involvement of the spine and sacroiliac joints which frequently leads to significant spine deformity and disability. The development of effective therapies for AS, particularly with anti-tumor necrosis factor agents, has resulted in improved symptoms and functions for many patients, and clinical research increasingly suggests that effective therapy can also prevent destruction in the spine and other structures. Recent focus of disease classification in AS has emphasized that many individuals with features of inflammatory back pain but no visible changes on plain x-rays have active inflammatory disease when imaged with magnetic resonance imaging (MRI). Recent studies indicate that individuals with "non-radiographic" spondylitis can also respond to anti-inflammatory therapies. Several new agents are also showing promise for treatment of AS. These developments represent a significant advance in the management of this debilitating condition.

Introduction

Recent significant advances in the diagnosis and treatment of AS are leading to a shift in emphasis toward the goal of achieving low disease activity or remission. New classification criteria developed by the Assessment of SpondyloArthritis International Society (ASAS) that distinguish radiographic axial spondyloarthritis (SpA) from non-radiographic axial spondyloarthritis (nr-axSpA) will likely also further the goal of initiating treatment earlier in the course of disease to prevent loss of function. In light of these developments, this review aims to provide an update on AS, with an emphasis on advances in classification and new therapeutic approaches.

AS is an inflammatory disease involving primarily the axial skeleton and sacroiliac joints. Other musculoskeletal manifestations of the disease include peripheral arthritis and enthesitis. Extra-articular disease includes anterior uveitis, osteoporosis, cardiac disease with primarily valvular involvement, renal disease, lung disease, gastrointestinal disease, and skin disease. AS has a male predominance with a male-to-female ratio of 3:1. The peak age of onset is typically in the second or third decade of life. AS is strongly associated with human leukocyte antigen (HLA)-B27, with the prevalence of the B27 allele approaching 90% worldwide, but the pathogenic mechanism underlying this association remains unclear. Proposed mechanisms include the arthritogenic peptide theory, HLA-B27 heavy-chain homodimer formation, and HLA-B27 misfolding and the unfolded protein response. HLA-B27 is a major histocompatibility complex class I allele that is widely prevalent in the population depending on ethnicity, and the prevalence of AS correlates with the frequency of HLA-B27 in different populations. In the US, the age-adjusted prevalence of HLA-B27 is estimated to be 6.1% from the National Health and Nutrition Examination Survey (NHANES) study [1]. However, less than 5% of carriers of HLA-B27 develop AS. Among Caucasians, 7.5% of the population carries of HLA-B27 whereas 0.13% of Caucasians in the US develop the disease. On the other hand, in Caucasians with AS, 90% to 95% are carriers of HLA-B27. In contrast, African-Americans and Japanese

have a very low frequency of HLA-B27 and a very low disease prevalence. Estimates of the prevalence of AS worldwide range from approximately 0.5% to 0.07% [2,3].

Diagnosis and classification

Diagnosis of AS is based on the modified New York diagnostic criteria that were initially proposed in 1984 [3]. The diagnosis is based primarily on evidence of sacroilitis on radiographic imaging, a finding that can take many years to develop. To have definite AS, there must be unilateral grade 3 or 4 sacroilitis or bilateral grade 2 to 4 sacroilitis and clinical symptoms of AS. In an effort to identify patients with axial SpA earlier, new classification criteria were established by the ASAS in 2009 [4]. This classification divides axial SpA into radiographic and non-radiographic SpA. The term non-radiographic SpA (nr-axSpA) is somewhat misleading as it refers to the absence of sacroilitis on x-ray but includes patients with sacroilitis on MRI. According to the ASAS classification criteria, patients with low back pain for 3 or more months and an age of onset before 45 years can meet criteria for axial SpA via either an "imaging arm" or a "clinical arm". In the imaging arm, sacroilitis must be present based on traditional radiographic changes or based on MRI changes. In addition, one or more typical SpA features must be present. In the clinical arm, in the absence of any radiographic or MRI abnormality, patients must test positive for HLA-B27 in addition to having at least two other typical SpA features to be diagnosed with axial SpA. Although these criteria extend classification criteria to non-radiographic disease, they do not distinguish it from radiographic disease. When this classification is used, patients with established radiographic changes are classified as AS, whereas those without are defined as nr-axSpA. Patients with a diagnosis of AS by the modified New York criteria also meet the ASAS criteria. In nr-axSpA, there may be a less-marked male predominance. In studies looking at differences between AS and nr-axSpA, 65% to 77% of the AS patients were men, whereas only 31% to 48% of the nr-axSpA patients were men [5-7].

It remains unclear whether AS and nr-axSpA are separate diseases or diseases within a spectrum and this issue is an area of ongoing interest. In studies comparing AS with nr-axSpA, similar clinical disease activity and functional status have been found after adjusting for differences in disease duration and gender differences. In addition, nr-axSpA seems to have similar, though probably not equivalent, responses to the treatments used for AS. These observations support the idea that the two entities reflect a spectrum of the same disease. For example, the group of patients with nr-axSpA appears to have lower C-reactive protein (CRP), higher female predominance, less structural damage in the spine and may not progress to AS for many years [8].

Disease activity measures

An international task force was recently formed to determine recommendations for treatment targets to improve management of axial and peripheral SpA in clinical practice. Guidelines developed by the task force focused on treating to a target of low disease activity or clinical remission [9]. Measures used to assess disease activity in spondylitis include assessment of patient-reported inflammatory symptoms and acute-phase reactants (erythrocyte sedimentation rate [ESR] or CRP). Validated composite measures of disease activity are the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) plus acute-phase reactants and the Ankylosing Spondylitis Disease Activity Score (ASDAS). The BASDAI is composed of six patient-reported variables evaluating clinical symptoms of inflammation, and the ASDAS is composed of both patient-reported variables and laboratory evaluation of inflammation using CRP and ESR. Other activity measures used include evaluation of functional status using the Bath Ankylosing Spondylitis Function Index (BASFI) or evaluation for partial remission using the ASAS. The Bath Ankylosing Spondylitis Metrology Index (BASMI) is also used for quantitative monitoring of patients over time in clinical practice and includes measurement of occiput-to-wall and modified Schober's and thoracic expansion. MRI is now used in research studies and in clinical practice for early detection of sacroilitis. This modality provides the ability to diagnose SpA before disease damage is seen radiographically. MRI has also been used in clinical research studies to assess treatment efficacy, and it has been suggested that MRI will likely be increasingly useful in clinical practice as a disease activity measure for nr-axSpA.

General treatment considerations

The impact of AS is significant. Active disease has been correlated with reduced quality of life and work disability, and progressive syndesmophyte formation can result in greatly reduced functional status. The goal of both non-pharmacologic and pharmacologic therapy is to halt disease progression as determined by clinical symptoms, radiographic disease, and serologic inflammatory markers. Exercise remains the cornerstone of non-pharmacologic intervention. Multiple systematic reviews and studies have shown that exercise can improve pain, physical function, spinal mobility, and patient global assessment. In addition, supervised physical therapy with individual or group exercise is better than home exercise in improving functional status [10]. Patient education and counseling about abstinence and smoking cessation are also key non-pharmacologic interventions for AS because cigarette

smoking has been shown to be an independent risk factor for radiographic progression [11,12].

Pharmacologic treatments have generally focused on targeting inflammation. However, as for AS, it is not clear whether syndesmophyte formation is directly linked to inflammation. Prior studies have shown progression of syndesmophytes despite disease remission based on inflammatory markers and clinical symptoms. On the other hand, treatment with continuous non-steroidal anti-inflammatory drugs (NSAIDs) has shown decreased progression of syndesmophytes despite ongoing inflammatory pain symptoms and disease activity. Assessment of patient's risk factors for disease progression is important in determining treatment therapy. Independent risk factors for radiographic progression include elevated inflammatory markers (CRP), presence of syndesmophytes at baseline, cigarette smoking, and longer duration of disease [11]. Along the same lines, favorable indicators for treatment response include elevated CRP, short symptom duration, younger age, and evidence of inflammation on MRI. Inflammatory markers should be assessed at each visit over time to determine treatment efficacy. Radiographs of the cervical and lumbar spine at baseline and then repeated at a minimum of two years are helpful in determining structural disease damage and progression. Repeating radiographs prior to that time frame would be unlikely to show radiographic change.

Specific interventions
Non-steroidal anti-inflammatory drugs
NSAIDs remain the first-line treatment for AS. NSAIDs were the first class of drugs to show improvement in radiographic progression in AS. In a 2-year randomized controlled trial, continuous use of NSAIDs versus on-demand use was compared. The primary outcome evaluated was radiographs of the lumbar and cervical spine scored according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) at baseline and at 2 years. The study found a significant reduction in radiographic progression in the continuous-use group compared with the on-demand group [13]. Another study evaluated NSAID use in both AS and non-radiographic axial SpA [14]. Patients with a high NSAID intake (defined using an NSAID index score of at least 50) had less radiographic progression based on mSASSS compared with low NSAID intake (NSAID index of less than 50). The effect on radiographic spinal progression was more dramatic in patients with active disease and high CRP in addition to patients with baseline syndesmophytes. Interestingly, in nr-axSpA, there was no effect on radiographic spinal progression, which was thought to be due to low bone formation activity in this group of patients.

Current recommendations are to treat symptomatic AS patients with continuous NSAIDs at an adequate therapeutic dose. Patients with active AS should be trialed on at least two NSAIDs for at least 4 weeks or more for an adequate trial. All NSAIDs have been shown to be effective, but cyclooxygenase (COX)-2-selective NSAIDs should be considered in patients with peptic ulcer disease or inflammatory bowel disease and with caution in patients at risk for cardiac disease. It should also be noted that hypertension, abdominal pain, and dyspepsia were more frequent but not statistically significant in the continuous-use groups and these side effects should be discussed with the patient.

Tumor necrosis factor inhibitors
Conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulfasalazine have not been shown to be effective in axial SpA. For patients who have had inadequate response to at least two NSAIDs used for 4 weeks or more, tumor necrosis factor-alpha (TNF-α) inhibitors are the second line of treatment for AS. Multiple TNF-α inhibitors, including etanercept, adalimumab, golimumab, infliximab, and certolizumab, have been shown to be efficacious in active AS [15-19]. In these studies, approximately 60% of patients responded to TNF-α inhibitors. In patients who have lost efficacy over time to the initial TNF-α inhibitor, switching to a second anti-TNF agent has been shown to be beneficial [20]. Factors that predict response to TNF-α inhibitors include short duration of disease and early treatment, active disease based on elevated CRP and inflammation on MRI, and response in the first 3 to 6 months of treatment. In the past, studies of TNF-α inhibitors in AS have not shown improvement in radiographic progression despite improvement in clinical symptoms and inflammatory markers [21-23]. However, more recently, treatment with TNF-α inhibitors was found to reduce radiographic progression in AS patients when initiated early in disease and with longer duration of follow-up [12].

Rituximab
Rituximab is an anti-CD20 monoclonal antibody that may have some efficacy in TNF-α inhibitor-naïve patients with active AS. In a prospective open-label trial, rituximab given 1000 mg intravenously at weeks 0 and 2 was evaluated in 20 patients with active AS [24]. Half of these patients were TNF-α inhibitor-naïve, and half were TNF-α inhibitor failures. In the TNF-α inhibitor failures, there was no significant difference in outcomes compared with placebo. In the TNF-α inhibitor-naïve group, 50% achieved ASAS20 response (at least 20% improvement in the ASAS response criteria), 40% achieved ASAS40 response (at least 40% improvement in the ASAS response criteria), 30% achieved partial remission based on ASAS

criteria, and 50% achieved a BASDAI50 response (at least 50% improvement in the BASDAI response criteria). In a 1-year follow-up, of the nine patients who were responders, five flared and were retreated with a second course of rituximab and had similar improvement in BASDAI, ASDAS, and CRP compared with the first treatment [25]. This study was too small to show statistical significance and these responses are less than those seen with anti-TNF agents. Thus, further larger placebo-controlled trials will be required to determine what, if any, role rituximab has in AS therapy.

Agents with minimal efficacy
As noted previously, conventional DMARDs are generally ineffective for AS, and about 40% of patients with active AS do not respond to TNF inhibitors. Multiple other biologic agents have now been studied in AS and have shown minimal efficacy despite their efficacy in other inflammatory rheumatic diseases such as rheumatoid arthritis.

Abatacept
Abatacept is a biologic construct of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that inhibits T-cell co-stimulation by blocking the binding of B7(CD80/86) on the antigen-presenting cell and CD28 on the T cell. In a small open-label pilot study, abatacept was found to be ineffective in both TNF inhibitor-naïve and TNF inhibitor-refractory patients with active AS [26].

Anakinra
Anakinra is an interleukin-1 (IL-1) antibody that was evaluated in 20 NSAID-refractory patients with active AS [27]. As a group, there was no improvement noted in mean BASDAI, BASMI, BASFI, general pain, patients' and physicians' global assessments, CRP, or MRI scores.

Tocilizumab
Part 1 of the BUILDER-1 trial was a randomized, placebo-controlled trial of 102 patients who were TNF-naïve and treated with tocilizumab 8 mg/kg versus placebo for 12 weeks [28]. The primary efficacy end point was the proportion of patients achieving ASAS20 at 12 weeks. Despite improvement in both CRP and IL-6 levels, the study did not demonstrate efficacy of tocilizumab in TNF-naïve patients with AS. The study was initially intended to be a two-part study with an additional phase III study (BUILDER-2) in inadequate TNF responders but these studies were terminated early after negative results from part 1 of the BUILDER-1 study.

Sarilumab
Sarilumab is a fully human anti-IL-6 receptor (anti-IL-6Ra) monoclonal antibody that was shown in phase II studies to be effective in rheumatoid arthritis and was recently evaluated for efficacy in AS. The ALIGN study ("A Randomized Double Blind-placebo Controlled Dose Ranging Study to Evaluate the Efficacy and Safety of SAR153191 in Patients With Ankylosing Spondylitis") was a large multi-center study with 301 patients who were treated with various doses of sarilumab versus placebo [29]. At week 12, there was no statistically significant difference in ASAS20 response between placebo and any of the sarilumab doses.

Treatment response in non-radiographic disease versus radiographic disease
Treatment of non-radiographic axial SpA is approached similarly to axial SpA. First-line treatment consists also of NSAIDs. In patients with an inadequate response to NSAIDs, TNF-α inhibitors are recommended as second-line agents. Studies on etanercept, infliximab, adalimumab, and certolizumab have demonstrated efficacy in non-radiographic spondylitis [19,30-33]. Treatment responses have been similar to, if not better than, those seen with AS but this may be due to differences in disease duration and early treatment. ABILITY-1 was the first study that evaluated efficacy of TNF-α inhibitor in nr-axSpA based on ASAS axial SpA criteria [33]. Prior to this trial, other studies in etanercept and adalimumab demonstrated efficacy in early AS disease but used different disease definitions. In the ABILITY-1 study, significantly more patients in the adalimumab group achieved ASAS40 at week 12 compared with patients in the placebo group (36% versus 15%, $P < 0.001$). These results are similar to the ASAS40 at week 12 in AS patients treated with adalimumab compared with placebo (39.9% versus 13.1%, $P < 0.001$) [16]. Based on results from ABILITY-1, adalimumab was approved in 2012 for treatment of nr-axSpA in Europe. RAPID-axSpA ("Certolizumab Pegol in Subjects With Active Axial Spondyloarthritis") is another placebo-controlled trial that examined the efficacy of certolizumab in patients with axial SpA [18]. At week 12, ASAS20 response rates were significantly higher in the treatment arms with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared with placebo (57.7 and 63.6 versus 38.3, $P \leq 0.004$). A recent meta-analysis compared the efficacy of all TNF-α inhibitors in nr-axSpA with the efficacy in AS [34]. In the unadjusted analysis, patients with non-radiographic disease had a statistically significant lower improvement in disease activity and function than those with AS. However, after adjustment for differences in disease duration and disease severity using publication year as a covariate, there was no significant difference in efficacy found between patients with AS and those with nr-axSpA. Although there are limitations to meta-analyses, this recent study supports the use of TNF-α inhibitors in patients with non-radiographic disease.

Prior studies in AS have found decreased bone formation with NSAIDs alone, and other studies have demonstrated decreased inflammation with TNF-α inhibitors. Surprisingly, until recently, there has been no direct comparison to determine whether early combination therapy with NSAIDs and TNF-α inhibitors will target both inflammation and bone formation better than initial NSAID therapy alone. INFAST was a two-part study evaluating the efficacy of early treatment with TNF-α inhibitors prior to NSAID failure and whether efficacy could be better maintained with NSAIDs after TNF-α inhibitor withdrawal. The first part of the study compared infliximab plus naproxen with naproxen monotherapy in patients with early disease of less than 3 years' duration who were NSAID-naïve or had been on a submaximal NSAID dose [35]. The infliximab-plus-naproxen group had significantly more patients achieve ASAS partial remission at week 28 compared with the naproxen-monotherapy group (61.9% versus 35.3%, *P* = 0.002). As a comparison, in the initial efficacy study of infliximab in AS, ASAS partial remission at week 24 was only 24.4%. However, the mean disease duration for AS was 10 years. Of note, the response rate for naproxen monotherapy was also quite high, and it remains to be seen whether similar response rates would be seen in clinical practice with treating very early disease. From INFAST part 1, starting TNF-α inhibitor with NSAIDs early may significantly increase remission response, but risk and benefits would need to be weighed about long-term TNF-α inhibitor therapy in a young population. INFAST part 2 attempted to address this concern and evaluated whether partial remission could be better maintained after TNF-α inhibitor withdrawal with naproxen compared with no treatment at all [36]. There was no significant difference found at 6-month follow-up, but the study was too short to detect any difference since initial treatment response persisted in both arms. Future studies on how to maintain patients after TNF-α discontinuation will be of great interest.

New targets and treatments

The IL-17/IL-23 axis has been of recent interest as a potential target in SpA. Sherlock and colleagues [37] demonstrated entheseal-resident T cells that responded to IL-23 by releasing IL-17 and IL-22. IL-17 induced local inflammatory change, and IL-22 induced osteoblast-mediated bone remodeling. Studies in mice have suggested that IL-23 overexpression alone may result in enthesitis and in joint disease that resembles AS in humans. These studies, which focus on the role of entheseal T cells, have helped to generate hypotheses that may provide a unified explanation for the predilection for disease to occur at entheses as well as the presence of new bone formation in these sites of inflammation.

Il-17A/Secukinumab

Secukinumab is a fully human anti-IL-17A monoclonal antibody. In a small proof-of-concept study with 30 patients with active AS, patients were randomly assigned to receive secukinumab (2 × 10 mg/kg) versus placebo in a 4:1 ratio [38]. Primary end point of ASAS20 at week 6 was achieved in 14 (61%) of 23 patients in the secukinumab arm compared with 1 (17%) of 6 patients in the placebo arm. Of note, patients with prior inadequate response to a TNF treatment were allowed to be in the study. From these preliminary results, secukinumab appears to act rapidly and may be a future option for AS patients who fail TNF treatment. A 16-week efficacy study for secukinumab infusion and injection with long-term safety and efficacy follow-up at 2, 3, and 5 years is ongoing (NCT01863732, NCT02008916, NCT01358175, NCT01649375).

Anti-IL12/23 – Ustekinumab

Ustekinumab is a fully human monoclonal antibody that blocks IL-12 and IL-23 cytokine activity through binding of the p40 protein subunit of these cytokines. The TOPAS study (*UsTekinumab* for the treatment Of Patients with active Ankylosing Spondylitis) was a single-arm proof-of concept study involving 20 patients who were all treated with ustekinumab [39]. The study excluded patients with a history of non-response to TNF-α-blocking therapy. The primary end point of ASA40 at week 24 was achieved in 13 (65%, 95% confidence interval 41% to 85%) of 20 patients. The proportion of patients achieving ASAS40 in this trial is significantly higher than the reported ASAS40 response from prior TNF-α inhibitors, which is around 40%. Future larger studies comparing this agent with placebo or even TNF inhibitors will be of great interest.

PDE4 – Apremilast

Apremilast is an oral phosphodiesterase 4 inhibitor that has been shown in a double-blind, placebo-controlled phase II study to have potential efficacy in AS [40]. This exploratory study was too small (n = 38) and too short in duration to demonstrate statistical significance. However, the study did demonstrate improvement in both the primary end point (change in BASDAI at week 12) and all other clinical assessments (BASFI, BASMI, ASAS20, and ASAS40) compared with placebo, suggesting that this may be a useful target in this disease. Future longer-term studies are needed to determine its efficacy and safety profile in AS.

Ongoing studies

Several current studies could help identify new targets and novel indications for established treatments in AS. Tofacitinib is an orally bioavailable small-molecule JAK

kinase inhibitor that was approved for treatment of rheumatoid arthritis in November 2012 and is being studied for treatment in active AS (NCT01786668). There is also an ongoing study on golimumab and efficacy in early axial SpA (NCT01453725). Trials evaluating anti-TNF withdrawal in stable, low-disease AS and in nr-axSpA are also in progress (NCT01604629, NCT01610947, NCT01808118).

Recent advances in diagnosing early spondylitis emphasize that our understanding and the management of AS and related diseases will continue to evolve. For example, similarities and differences in treatment response between radiographic and non-radiographic spondylitis may reflect that these two conditions represent distinct, but overlapping and related, disease processes. In this regard, additional work is needed to clarify the relation between nr-axSpA and AS, particularly as it relates to the development of AS-related disability and in defining the optimal timing and kind of treatment for each entity. For example, does early treatment of nr-axSpA prevent the development of significant radiographic changes or lead to improved functional outcomes? This is of particular relevance because, based on the newer classification criteria, recognition and impetus to treat nr-axSpA are likely to increase, as are estimates of the prevalence of axial spondylitis. The development of effective new treatments for AS and related inflammatory spondylitis represents real and significant progress in the management of what for many patients has been a chronically painful and progressively debilitating disease. Determining the most beneficial and cost-effective application of these treatments is a work in progress.

Abbreviations

ABILITY-1, A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects With Axial Spondyloarthritis; AS, ankylosing spondylitis; ASAS, Assessment of Spondylo-Arthritis International Society; ASAS20, at least 20% improvement in the Assessment of SpondyloArthritis International Society response criteria; ASAS40, at least 40% improvement in the Assessment of SpondyloArthritis International Society response criteria; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BUILDER 1, A Study of RoActemra/Actemra [Tocilizumab] in Patients With Ankylosing Spondylitis Who Have Failed Treatment With NSAIDs; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; IL, interleukin; INFAST, Infliximab as First-Line Therapy in

Patients with Early Active Axial Spondyloarthritis Trial; MRI, magnetic resonance imaging; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; nr-axSpA, non-radiographic axial spondyloarthritis; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthritis; TNF-α, tumor necrosis factor-alpha.

Disclosures

The authors declare that they have no disclosures.

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