

Overview of Drug Therapy for Spondyloarthritis

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Introduction

The axial spondyloarthritides (axial SpA) are a related group of disorders prototypically represented by Ankylosing Spondylitis (AS). Reactive arthritis, psoriatic arthritis, enteropathic arthritis and undifferentiated spondyloarthritis are also included in this family. The prevalence of this group of disorders roughly approximates that of ankylosing spondylitis, affecting 1% of the population [1]. Recent updates in classification according to the Assessment of SpondyloArthritis International Society (ASAS) are gaining traction in Rheumatology practice, however some disagreement between clinical diagnosis and ASAS remain [2]. Moreover, ASAS guidelines for classification are shaping the treatment of these conditions [3,4].

Agents used in the management of spondyloarthritis include Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), selected non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs), and most recently the anti-tumor necrosis factor biologic DMARDs (biologics) [3]. Though the agents available for treating SpA are similar to those employed in the treatment of rheumatoid arthritis, differences in treatment outcomes for these medications between the two diseases lead to important distinctions. Initial management of these conditions is accessible to non-rheumatologists and ideally will be instituted concomitantly with referral for confirmation of diagnosis and, if needed, adjustment of the treatment regimen.

Additionally, non-pharmacologic and procedural therapies play an important role in the management of SpA/AS. Patient education is always recommended and disease-based patient groups may also provide benefit [3]. Physical therapy and exercise generally lead to improved symptom control; patient directed exercise is acceptable with physical therapy including supervision of exercise is preferred [3]. Corticosteroid injections can be given at peripheral sites of inflammation; however their use is not recommended in axial disease due to lack of evidence for efficacy [3]. Referral to orthopedic surgery should be considered in patients with refractory hip pain and is mandatory in AS patients with acute spinal fracture [3].

Herein the approach to the treatment of axial SpA drawing from the perspective of ankylosing spondylitis will be reviewed. The emphasis is on medical therapies employed according to ASAS guidelines.

Outcome Measures in Ankylosing Spondylitis Trials

Outcome measures used in the assessment of ankylosing spondylitis clinical trials are often used to frame the discussion of results. Common scoring systems include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [5] and the Assessments in Spondyloarthritis Society, formerly Assessments in Ankylosing Spondylitis Working Group, (ASAS) criteria [6]. The Ankylosing Spondylitis Disease Activity Score (ASDAS), developed in 2009, is the newest tool for measuring disease activity [7].

The BASDAI was introduced in 1994 and remains widely used. It is a self administered 6 question instrument that patients are able to complete in a few minutes. It includes features of disease activity including morning stiffness, fatigue, spinal pain, and appendicular joint pain, producing scores ranging from 0 to 10 with higher scores indicating increasing levels of disease activity [5].

The ASAS criteria were introduced in 2001 and are similar to the ACR criteria for improvement in Rheumatoid arthritis in that specific cut-offs are used to indicate percent improvement. For example, the ASAS 20 indicates an improvement in 20% or more of 3 of 4 domains including patient global assessment, pain, function, and inflammation without worsening of the remaining domain. It approximates an ACR 20 for ankylosing spondylitis and other forms of axial SpA [6].

The most recent disease activity and improvement score was introduced by ASAS in 2009: the Ankylosing Spondylitis Disease Activity Score (ASDAS) [7]. It is analogous to the DAS used in rheumatoid arthritis and includes measures of back pain, morning stiffness, peripheral joint pain and swelling, and a patient global assessment. Similar to DAS either C-Reactive Protein (CRP) or Erythrocyte Sedimentation Rate (ESR) can be used for the acute phase reactant; however the ASDAS based on CRP is preferred [7]. Scores greater than 3.5 indicate very high disease activity and scores below 1.3 indicate inactive disease or remission. Changes in ASDAS produced by therapy of 1.1 units indicate a clinically relevant improvement and 2.0 units or more indicate a major clinical improvement.

Though the disease activity constructs vary, the use of standardized outcome measures mirrors that previously described for rheumatoid arthritis [8]. Each captures the status of clinical domains relevant to the treatment of ankylosing spondylitis and understanding the language of AS outcome measures is important to understanding the magnitude of treatment effects produced by medications in AS. At present ASAS-20 and BASDAI remain widely used but increased use of the ASDAS is anticipated as clinical trialists become more familiar with it.

First Line Therapy: NSAIDs

The NSAIDs are a widely used to treat a variety of musculoskeletal disorders. These medications exert their anti-inflammatory effect through the inhibition of Cyclooxygenase (COX) enzymes required in the production of prostaglandins and leukotrienes. Notable side effects include but are not limited to increased risk of myocardial infarction and gastrointestinal bleeding [9]. These risks are reduced but not eliminated as the specificity for inhibition of the COX-2 isoform increases. Previous comprehensive reviews of long term use of NSAIDs in AS estimate the risk of any serious adverse effect from NSAIDs at 1% [9]. This finding combined with accumulating evidence for a disease modifying effect of NSAID use on spinal progression has shifted the risk: benefit ratio in favor of NSAIDs for the treatment of axial SpA.

Accordingly, recent guidelines published by ASAS/EULAR recommend NSAIDs are first line agents for treatment of axial and

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peripheral manifestations of spondyloarthritis [3]. Before moving on to other therapeutic agents, the guidelines endorse a trial of at least 2 NSAIDs over a 4 week period at the maximum recommended dose for each agent to ensure the maximum anti-inflammatory effect [3]. Examples include ibuprofen 800 mg three times daily or indomethacin 50 mg three times daily.

Experience with NSAIDs in spondyloarthritis suggests a differential effect compared to the experience in rheumatoid arthritis. In rheumatoid arthritis, NSAIDs improve signs and symptoms of active disease but have never been shown to have disease modifying properties. Studies of selected NSAIDs in spondyloarthritis demonstrate short term efficacy and suggest a potential to stop or reduce radiographic progression.

Sieper et al. performed a randomized non-inferiority trial of celecoxib compared to diclofenac over 12 weeks in the treatment of ankylosing spondylitis which typifies the favorable short term clinical response produced by NSAIDs [10]. Changes in a visual analogue pain scale and the BASDAI were similar in all groups, though statistically better on celecoxib 200 mg twice daily and diclofenac 75 mg twice daily compared to celecoxib 200 mg daily. ASAS 20 was achieved by 46% of patients on celecoxib 200 mg daily, 59.7% of patients on celecoxib twice daily, and 60.2% of patients on diclofenac 75 mg twice daily. Gastrointestinal side effects were reduced during the study period for both doses of celecoxib compared to diclofenac, consistent with the increased selectivity for COX-2 inhibition of celecoxib over diclofenac.

Wanders et al. were the first to report the potential for NSAIDs to reduce radiographic progression in patients with ankylosing spondylitis [11]. 215 patients with AS were studied for 2 years and randomized to receive continuous or on-demand NSAID treatment with celecoxib starting at 100 mg twice daily with a maximum allowed dose of 200 mg twice daily. In case of adverse event or inefficacy patients were permitted to change to an alternate NSAID but were asked to maintain the initially allocated treatment strategy; this approach led to a significant difference ($p < 0.0001$) in average daily dose between the continuous treatment group (243 mg) compared to the on-demand cohort (201 mg). Radiographic progression as measured in the spine occurred in 45% of the on-demand NSAID patients compared to 22% of the continuous NSAID patients ($p = 0.002$).

More recently, Poddubnyy et al. provided additional evidence of long-term reduction of radiographic spinal progression by NSAIDs in a report based on two year data on 164 patients with axial SpA (88 patients with AS and 76 with non-radiographic axial SpA) from the German Spondyloarthritis Inception Cohort (GESPIC). Patients with AS using high levels of NSAID, defined as ASAS NSAID Index > 50 , compared to low levels of NSAID intake (Index < 50) had a lower likelihood of radiographic progression (OR = .15; $p = -0.045$, 9% CI 0.02 to 0.96) [12]. No difference was observed in non-radiographic axial SpA patients [12]. COX selectivity of the NSAID did not impact the degree of radiographic progression [12].

Traditional DMARDs

Sulfasalazine and methotrexate are traditional DMARDs considered for the treatment of ankylosing spondylitis and other forms of SpA. These agents are commonly used individually or in combination to treat rheumatoid arthritis based on their proven efficacy. These agents have been much less effective in the treatment of ankylosing spondylitis and other SpA, however, as reflected in current guidelines for SpA therapies [3,4].

In contrast to rheumatoid arthritis, where methotrexate is

considered the gold standard therapy, current SpA guidelines do not recommend methotrexate for the treatment of axial or peripheral manifestations [3,4]. Despite lack of evidence for efficacy in axial disease and questionable effectiveness in peripheral SpA, methotrexate has been re-evaluated periodically in SpA. The most recent investigation of methotrexate use in ankylosing spondylitis was published in 2007 [13]. Injected methotrexate was administered in open fashion to 20 patients with AS over 16 weeks. Outcome measures included the number of patients achieving ASAS 20 and change in BASDAI over the study period. Only 25% of patients reached ASAS20 response and no change was observed in BASDAI over 16 weeks. A subgroup analysis of 7 patients with peripheral arthritis showed a non-significant improvement in the number of swollen joints with arthritis.

A new Cochrane review of the use of methotrexate in AS was released in 2013, updating the prior review published in 2006. Since the 2006 review, three trials evaluating the use of methotrexate in AS were reported, including a total of 116 patients. Of the new trials, the authors found a benefit for treatment with methotrexate compared to no methotrexate in only one; this trial yielded a number needed to treat for benefit (NNT) for methotrexate over placebo of 3 [14]. The authors' concluded there is not enough evidence of benefit to support the use of methotrexate in the treatment of AS and that larger high quality randomized trials are needed [14].

The experience of sulfasalazine in axial SpA is similar to methotrexate; it is not recommended in the most recent ASAS guidelines for axial disease. Sulfasalazine is an important drug for peripheral manifestations, however, and is recommended before a trial of TNF antagonists when NSAIDs have failed [4]. Similar to methotrexate, the potential role for sulfasalazine in the treatment of axial manifestations has been revisited due to its persistent use in AS in clinical practice. The most recent Cochrane review of sulfasalazine in ankylosing spondylitis occurred in 2005. The AS patients from 11 studies included in the analysis showed some benefit in reduced morning stiffness and ESR, however no improvements were observed in pain, physical function, enthesitis, spinal mobility, and global assessments by both patient and physician [15].

Since the last Cochrane review, the sole trial published on sulfasalazine in AS was the Ankylosing Spondylitis Study Comparing Enbrel with Sulfasalazine Dosed Weekly (ASCEND) trial. ASCEND was a 16 week randomized, double-blinded, placebo controlled study of axial and peripheral responses to enbrel 50 mg weekly or sulfasalazine with a target dose of 3 g daily in patients with AS [16]. The primary outcome measure was the ASAS20 score. 75.9% of enbrel patients achieved ASAS20 compared to 52.9% of sulfasalazine patient ($p < 0.0001$). Enbrel was also more effective than SSZ in secondary outcome measures of ASAS40 and BASDAI. Though outperformed by enbrel, more than half of sulfasalazine-treated patients achieved the primary endpoint, suggesting there may yet be a role for sulfasalazine in axial disease.

Tumor Necrosis Factor Inhibitors

Multiple trials have demonstrated the efficacy of the anti-tumor necrosis factor biologic drugs in the treatment of ankylosing spondylitis. Though no direct comparisons of these agents have been performed, etanercept, infliximab, and adalimumab seem to produce similar clinical responses with comparable side effect profiles in SpA [17]. Recent positive experience with golimumab in a randomized double blind placebo controlled trial adds it to the list of anti-TNF- α agents effective in the treatment of ankylosing spondylitis [18].

ASAS guidelines recommend TNF- α antagonists for the treatment of axial and peripheral manifestations of ankylosing spondylitis and other SpA. In the case of axial disease, anti-TNF- α agents are recommended following the failure of adequate trials of 2 NSAIDs [3,4]. The guidelines do not specify a preference of anti-TNF- α drug for axial SpA, except in the case of axial enteropathic arthropathy where monoclonal antibodies may be preferred [3]. For peripheral SpA, a trial of sulfasalazine is generally preferred prior to the use of anti-TNF agents [3,4].

Optimal utilization of TNF- α antagonists in SpA continues to be refined. Younger age, male sex, higher levels of c-reactive protein and higher ASDAS scores all predict likelihood of response to anti-TNF- α drugs [19]. HLA-B27 positivity has also been reported to correlate with improved clinical response [20]. Patients with early disease, including those with non-radiographic axial SpA failing NSAIDs, obtain good clinical responses from TNF- α antagonists. Though somewhat counter-intuitive, patients with longer disease duration may also obtain benefit from these medications [21]. Lastly, the potential side effects of these drugs and the ability to maintain remission with lower dose regimens in some patients [22] will mandate that future guidelines address dose modulation of TNF- α blockers in the treatment of SpA.

Novel Therapeutic Approaches

Despite the favorable clinical responses produced by the NSAIDs, sulfasalazine, and the tumor necrosis factor antagonists, some patients with ankylosing spondylitis or other forms of spondyloarthritis will continue to have symptoms. Rheumatologists logically have turned to non-TNF antagonist biologics that have utility in rheumatoid arthritis for study in AS.

The largest studies of non-TNF biologics in AS include abatacept and rituximab. A 24 week open label pilot study of the T-cell costimulation inhibitor abatacept produced an ASAS 40 response in only 13% of TNF-inhibitor naïve patients and in 0% of TNF-inhibitor failure patients; ASDAS did not change significantly in either group [23]. A study of rituximab in AS patients was also performed using the rheumatoid arthritis dosing strategy: 1000 mg at baseline and in 2 weeks. 20 patients were included in the trial, 10 TNF naïve and 10 TNF failures. Only 10% of TNF failure patients achieved an ASAS 40 response compared to 40% of the TNF naïve patients [24].

The disappointing results with abatacept and rituximab have led investigators to explore the potential efficacy of other biologics in AS. Success has been reported in several cases of SpA due to various causes with inhibition of IL-6 and in small randomized controlled trials of inhibition of IL-17 (AS) and IL-12/IL-23 (psoriatic arthritis) [25]. Despite the promise of these approaches, current guidelines do not recommend the use of non-TNF inhibitor biologics in ankylosing spondylitis [4].

Conclusion

The treatment of axial spondyloarthritis is evolving with the release of new consensus guidelines occurring every few years. Implementation of ASAS guidelines in clinical practice is ongoing. Recommendations for drug therapy are made largely in the context of ankylosing spondylitis, simultaneously a subtype and prototypical form of axial spondyloarthritis. Distinctions in the management of axial and peripheral arthritis are made based on the differential performance of medications used in clinical trials of ankylosing spondylitis patients.

Nonsteroidal anti-inflammatory drugs should be used first for both axial and peripheral manifestations of spondyloarthritis and are

commonly employed by non-rheumatologists. Tumor necrosis factor inhibitors should be used in axial disease for NSAID failures because neither methotrexate nor sulfasalazine have consistently demonstrated efficacy in this situation. In peripheral disease, sulfasalazine but not methotrexate should typically be tried before moving to the TNF antagonists. There is currently no evidence of efficacy of the non-TNF antagonist biologic medications rituximab or abatacept in either axial or peripheral manifestations of spondyloarthritis. Early success has been reported with cytokine inhibition: IL-6, IL-12/23 and IL-17 but all of these approaches require additional study.

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