The current standard of care and the unmet needs for axial spondyloarthritis

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Abstract
The aim of this article is to explore the benefits and limitations of the established treatments for axial SpA (axSpA), including physiotherapy, NSAIDs, conventional synthetic DMARDs and biologic DMARDs such as TNF inhibitors (TNFis). It also briefly discusses the emerging role of anti-IL-17 therapy, which could be used as a valuable alternative to first-line biologic DMARD treatment or as a second-line treatment for patients who are inadequate responders to TNFi therapy, as evidenced by various studies. Exercise programmes improve health-related quality of life and hydrotherapy improves disease activity and functional parameters in AS. NSAIDs have been proven to substantially relieve symptoms in 70–80% of patients and enhance physiotherapy by reducing pain and stiffness. The role of NSAIDs in preventing radiographic progression remains unclear. The use of conventional synthetic DMARDs (csDMARDs) is limited to peripheral arthritis; there is insufficient evidence to support the use of csDMARDs for axial disease. TNFi therapy reduces the disease activity of axSpA, however, as not all patients respond to treatment in the same way, it is good to have other therapeutic options available. Finally, this article explores the potential for IL-17 inhibition in AS and introduces clinical data for secukinumab, a fully human monoclonal antibody targeting IL-17A.

Key words: axial spondyloarthritis, standard of care, unmet needs

Introduction
Axial SpA (axSpA) is categorized by regulatory authorities as non-radiographic axSpA (nr-axSpA) or AS (also known as radiographic axSpA). In this article, where possible, we will specify when studies relate to nr-axSpA or AS; however, it should be noted that these two categories have been shown to have highly similar clinical presentations [1, 2].

First-line therapy for axSpA: physiotherapy and NSAIDs
The optimal management of patients with SpA requires a combination of pharmacological and non-pharmacological approaches. To emphasize this point, best practice guidelines from the National Ankylosing Spondylitis Society recommend that patients should have access to a multidisciplinary team offering a full range of appropriate services in a timely manner [3]. Furthermore, quality standards from the British Society of Rheumatology (BSR) reinforce the importance of specialist-led multidisciplinary team clinics with a single point of contact responsible for the coordination of patient management [4]. The aim of all interventions should be to maximize quality of life and functional capacity. Initial assessment and regular monitoring enables treatment to be individualized, with patient wishes and expectations taken into consideration.

Joint recommendations from the Assessment of SpondyloArthritis international Society (ASAS) and the EULAR state that regular physical exercise and patient education should form the cornerstone of optimal treatment [5]. Furthermore, studies have shown that home-based exercise interventions can effectively improve health-related quality of life [6]. However, to improve adherence, supervised programmes (whether individual or in...
a group) may be more effective than home-based approaches [7]. In addition, contact with patient support groups should be encouraged, as this has the potential to improve motivation and compliance within the context of a long-term condition. A recent Cochrane review found that any exercise, whether supervised or home-based, is better than no exercise for improving movement and physical function [8]. The National Ankylosing Spondylitis Society has also highlighted the importance of access to hydrotherapy [3], which has been shown to improve disease activity and functional parameters in AS [9].

The BSR recommends that patient education should be personalized and available throughout care to help patients understand their condition and maintain involvement in self-management [4]. Self-management has been defined as ‘individual patient ability and competence regarding the management of symptoms, treatment, physical and psychosocial consequences, and the lifestyle changes inherent in living with a chronic condition’ [10]. As there is no cure, empowering patient self-management from the initial consultation onwards should be a key goal. Poor self-management increases the burden of disease on the individual and on health care resources [10].

Alongside physiotherapy, NSAIDs are the recommended first-line treatment for all symptomatic patients unless contraindicated [5]. Continuous treatment for patients with persistently active, symptomatic disease is preferred, where appropriate and safe [5]. Substantial relief of symptoms, including back pain and stiffness, has been reported by 70–80% of patients receiving NSAIDs [11]. These treatments also enhance physiotherapy because maximal reductions in pain and stiffness are required to achieve the optimal benefit from physiotherapy [11]. However, only one-third of patients achieve partial remission with NSAIDs alone, even among those with early, active axSpA (<3 years symptom duration) [12]. Predominant peripheral SpA, which shows only a partial response to conventional synthetic DMARDs, can also be managed with NSAIDs [13, 14].

The anti-inflammatory properties of NSAIDs may be more relevant than their analgesic properties for the treatment of axSpA. Studies have shown that CRP levels are modestly reduced within 12 weeks of treatment with diclofenac, celecoxib or naproxen [15, 16]. However, there is a lack of evidence supporting a role for NSAIDs in improving objective measures of inflammation as assessed by MRI [17, 18].

The role of NSAIDs in retarding radiographic progression in AS remains unclear, with no dedicated prospective studies. An early retrospective study suggested that continuous and prolonged use of phenylbutazone was associated with reduced spinal ossification [19]. Another study showed continuous rather than intermittent use of celecoxib yielded a better outcome regarding structural damage over a 2-year period [20]. However, another study failed to reproduce this effect in patients with AS and elevated baseline CRP: continuous use of diclofenac over 2 years did not result in any benefit on radiographic progression compared with on-demand use [21].

In 2015, a Cochrane review summarized the evidence for NSAIDs in axSpA. It concluded that ‘high to moderate quality evidence indicates that both traditional and cyclooxygenase-2-selective NSAIDs are efficacious for treating axSpA, and moderate to low quality evidence indicates harms may not differ from placebo in the short term’ [22]. The authors went on to state that the different NSAIDs used in axSpA are equally effective. With respect to disease control, they concluded that ‘continuous NSAID use may reduce radiographic spinal progression, but this requires confirmation’ [22].

The ASAS/EULAR recommend continuous use of NSAID therapy in patients who have symptomatic, active and persistent disease [5], although this often does not happen in practice because of safety concerns. Indeed, a major disadvantage of NSAIDs is their tolerability, in particular their effects on the cardiovascular system, gastrointestinal tract and kidneys [23–28]. Only two observational studies were identified in a recent systematic review of the safety profile of NSAIDs in axSpA: more is known about their tolerability from studies in other conditions [29].

NSAIDs and cyclooxygenase-2 inhibitors are associated with an increased risk of cardiovascular events [30]. Consequently, an assessment of cardiovascular risk should be performed before prescribing NSAIDs and cardiovascular risk factors should be addressed (e.g. through smoking cessation advice). Other important adverse effects include gastrointestinal and renal toxicity; these should be taken into consideration when prescribing NSAIDs [23–26, 31].

Therefore, while NSAIDs play a central role in the management of axSpA symptoms, these drugs are not effective in all patients and are associated with significant morbidities, which need to be carefully considered in each patient. Furthermore, their role in preventing radiographic progression is yet to be established [21, 22].

**Conventional synthetic DMARDs in axSpA**

Conventional synthetic DMARDs should only be used for peripheral arthritis: there is no evidence to suggest efficacy in the treatment of axial disease [5]. However, SSZ can be considered for patients with dominant peripheral arthritis in axSpA [5]. This is supported by a study of patients with axSpA and swollen joints at baseline in which the administration of SSZ for 3 months significantly improved BASDAI peripheral pain scores [32]. A trend towards an improved BASDAI score with SSZ has also been observed over 6 months in a subgroup of patients with AS and inflammatory back pain presenting with peripheral joint inflammation [33]. However, a Cochrane review concluded that there is insufficient evidence to support any benefit of SSZ in reducing pain, disease activity or radiographic progression or improving physical function and spinal mobility in AS [34]. There is also no evidence of efficacy for MTX monotherapy [35] and no
additional efficacy is conferred when MTX is combined with TNFi inhibitor (TNFi) therapy [36].

**TNFi therapy in axSpA**

According to the ASAS/EULAR recommendations, biologic DMARD therapy should be considered in patients who have persistently high disease activity (BASDAI score \( \geq 4 \) or ASDAS \( \geq 2.1 \)) despite conventional treatments (e.g. NSAIDs, steroid injection and SSZ as appropriate). In current practice this typically means starting with TNFi therapy [5]. TNFi therapies are indicated in patients with nr-axSpA with objective signs of inflammation by elevated CRP and/or MRI. Currently available TNFi therapies include (biosimilar) infliximab, golimumab, (biosimilar) etanercept, adalimumab and certolizumab pegol.

Although TNFis reduce the disease activity of axSpA for most patients, not all patients respond to treatment in the same way, so it is good to have other therapeutic options available.

A number of randomized controlled trials have been performed to evaluate the efficacy of TNFi therapies in axSpA (Table 1) [1, 5, 37–43].

In a seminal trial of patients with AS involving adalimumab, the response rate for a 20% improvement in ASAS criteria (ASAS 20) was 58.2% in the 208 participants in the active treatment arm [5]. Meanwhile, a trial of certolizumab pegol including patients with AS showed an ASAS 20 response rate of 57.7% in 218 participants [1]. Several trials have been conducted with etanercept, one of which demonstrated a response rate of \(~57\%\) among 138 individuals with AS [44]. In addition, 59.4% of 278 participants with AS involved in a golimumab trial achieved an ASAS 20 response [38]. Finally, an infliximab trial of patients with AS showed an ASAS 20 response rate of \(61.2\%\) among 201 individuals with AS [39].

Thus, although the majority of patients achieve a favorable outcome with TNFi therapy, not all patients respond equally well, highlighting that alternative treatments are needed. For patients who cannot tolerate or do not respond to their first TNFi therapy, or who stop responding after an initial response, the latest guidance from the National Institute for Health and Care Excellence (NICE) states that treatment with another TNFi or secukinumab is recommended [45]. ASAS/EULAR recommendations endorse the use of a second TNFi in the event the first fails [5]. A recent study of 1436 patients with AS who were started on TNFi therapy explored the effect in 432 patients of switching to a second biologic DMARD [46]. Those who switched had a shorter disease duration and higher BASDAI, BASFI and visual analogue scale global, pain and fatigue scores when their first TNFi agent was initiated than those who did not switch. The main reason for switching was a lack of response (56% of patients). Disease activity decreased significantly during the second and third treatment courses. However, those who switched treatment had a poorer clinical response and shorter drug survival than those who did not, and only half achieved treatment response [46]. Hence switching TNFi therapy can work, but diminishing returns are typical.

A study using both clinical and MRI assessments was conducted to explore the efficacy of infliximab compared with placebo in 40 HLA-B27-positive patients with MRI-determined early sacroilitis and symptoms of \(<3\) years duration [40]. The mean reduction in total MRI score was significantly greater with infliximab than placebo, suggesting that infliximab is effective in treating early sacroilitis. Notably, 55.6% of patients achieved partial remission, which is substantially higher than the 22% who achieved partial remission in a study of the same therapy in established disease, thereby indicating the benefit of early treatment in patients with more reversible disease [39, 40].

Numerous studies have demonstrated the efficacy of TNFi therapy in nr-axSpA [1, 40–43]. The key difference between these patients and those with AS is the absence of defined structural changes in the sacroiliac joint as detected on plain radiography. However, the burden of disease and the benefit derived from TNFi therapy are similar, and the latest guidance from the ASAS/EULAR [5], BSR [4] and NICE [45] allows for treatment of this subgroup according to criteria similar to AS.

Sustained drug-free remission is unlikely to be achieved following treatment with TNFi therapy, and numerous studies in AS have demonstrated the near inevitability of relapse upon discontinuation of treatment [44, 47, 48]. For example, in one study, 97.6% of patients had relapsed by 52 weeks after discontinuation of infliximab following 3 years of continuous treatment [47]. This appears to be the case even when patients are in remission or have a normal CRP level at the time of discontinuation. Similarly, even in early disease, relapse typically occurs after treatment discontinuation. In the Infliximab for Treatment of Axial Spondyloarthritis trial, patients with axSpA of \(<3\) years duration were treated with infliximab for 28 weeks and those in clinical remission were then discontinued: by week 52, 60% were no longer in remission [49]. In the ESTHER Trial (Frequency and duration of drug-free remission 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis), patients with axSpA were treated with etanercept for 1 year; those in clinical and imaging remission were then discontinued and followed for a further year. Only 8% were in drug-free remission at 2 years [50].

The effect of TNFi therapy on radiographic progression in axSpA is currently unclear. In one study following 334 patients treated with standard therapies for AS, 201 of whom received TNFi therapy, there was a 50% reduction in the odds of radiographic progression with the TNFi compared with standard therapy [51]. Another study conducted in patients with AS showed that TNFis are associated with a reduction in spinal radiographic damage [52]. However, numerous other studies have shown no effect of TNFi therapy on structural progression in AS [53–55]. One possible limitation of these studies is that TNFi therapy may be necessary for 4 years before any benefit on radiographic progression becomes apparent [56].
| Generic name | Trial       | Main inclusion criteria                                                                 | Number of patients in active arm/comparator arm | Primary endpoint | Primary endpoint vs PBO | References |
|-------------|-------------|-----------------------------------------------------------------------------------------|-----------------------------------------------|------------------|-------------------------|------------|
| Adalimumab  | ATLAS      | Active AS, inadequate response to glucocorticoids, NSAIDs, analgesics, MTX or SSZ         | 208/107                                       | ASAS 20 at week 12 vs PBO                            | 58.2 vs 20.6%         | [5]        |
| Certolizumab pegol | RAPID-axSpA | Active AS and nr-axSpA, elevated CRP levels and/or sacroiliitis on MRI, inadequate response to one or more NSAIDs | 111 (200 mg Q2W) 107 (400 mg Q4W/107) | ASAS 20 at week 12 vs PBO                            | 57.7% (200 mg Q2W) 63.6% (400 mg Q4W) vs 38.3% | [1]        |
| Etanercept  | Enbrel AS study group trial | Active AS                                                                                   | 138/139                                       | ASAS 20 at week 12 vs PBO                            | 57 vs 22%            | [37]       |
| Golimumab   | GO-RAISE    | Active AS with inadequate response to NSAIDs or DMARDs                                      | 138 (50 mg Q4W) 140 (100 mg Q4W/78)           | ASAS 40 at week 14 vs PBO                           | 59.4% (50 mg Q2W) 60.0% (100 mg Q4W) vs 21.8% | [38]       |
| Infliximab  | ASSERT      | Active AS, normal chest radiograph, negative for latent tuberculosis                          | 201/78                                        | ASAS 20 at week 24 vs PBO                            | 61.2 vs 19.2%         | [39]       |
| In patients with early/nr-axSpA | Infliximab | Recent-onset inflammatory back pain, HLA-B27-positive, MRI evidence of sacroiliitis               | 20/20                                         | Change in total MRI score at week 16 vs PBO         | −2.0 vs 0.0           | [40]       |
| Etanercept  | ESTHER      | Diagnosis of axSpA with symptom duration of ≤5 years, good or very good response to NSAIDs | 40/36                                         | Change in active inflammatory lesions in the SI joints and spine detected by MRI at week 48 vs SSZ | −5.7 vs −1.9          | [11]       |
| Infliximab  | INFAST (part 1) | Moderate to severe active axSpA with disease duration ≤3 years, not refractory to NSAIDs    | 105/51                                        | ASAS partial remission at week 28 vs PBO           | 61.9 vs 35.5%         | [12]       |
| Adalimumab  | —           | Active axSpA without radiographically defined sacroiliitis, refractory to NSAIDs            | 22/24                                         | ASAS 40 at week 12 vs PBO                            | 54.5 vs 12.5%         | [43]       |

Data taken from references 1, 5, 37-43. These data do not come from a direct head-to-head comparison. These data are from the pivotal placebo-controlled studies for each biologic listed; the study design, including inclusion/exclusion criteria and baseline characteristics may be different. "All patients enrolled into these trials had not received any anti-TNF therapy before randomization. "In addition to patients with AS (n=178), patients with nr-axSpA (n=147) were included in this trial; combined results were presented in this trial. ASAS: Assessment of SpondyloArthritis International Society; axSpA: axial spondyloarthritis; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks.
The impact of TNFi therapies on work participation in patients with AS has also been analysed in a recent systematic review [57]. Short-term productivity loss at work (presenteeism), absence from paid work and long-term employment status were assessed. Thirty-nine comparisons were reviewed, in nine studies, with most comparisons suggesting positive work outcomes with treatment, although these effects were not tested for statistical significance. Further studies are required to evaluate the effect of TNFi therapy on work-related outcomes in patients with long-standing AS.

Overall, TNFi therapy has been shown to be an effective treatment for axSpA, but there is an unmet need because not all patients respond well to or are able to tolerate these treatments. In addition, while no new safety signals were identified in patients with AS, TNFIs are associated with an increased risk of infections and other adverse events, so may not be tolerated or appropriate for all patients [58]. Hence there is a need for alternative treatment approaches that are safe and effective in axSpA.

**Anti-IL-17 therapy in axSpA**

Antagonism of the IL-17 pathway represents an alternative approach in disrupting inflammation by targeting the predominant cytokine made by Th17 cells as well as a number of other cells. IL-17 induces mesenchymal cells to release chemokines and growth factors, leading to the accumulation of neutrophils at the site of inflammation [59]. It has also been shown to augment collective neutrophil activity, as demonstrated by increased activity of neutrophil elastase, MMP-9 and myeloperoxidase after injection of recombinant IL-17 protein or stimulation with bacterial components [60–62]. Patients with AS exhibit an increased number of Th17 cells in their serum [63], and more Th17 cells were found in the facet joints of those with AS than in those with OA [64].

Secukinumab is a fully human mAb that selectively binds to IL-17A and is currently licensed for use in adult patients with active AS who have responded inadequately to conventional therapy; secukinumab is not licensed for use in nr-axSpA [65]. In a double-blind, placebo-controlled study of 30 patients with active AS, 59% of patients who received secukinumab achieved an ASAS 20 response at week 6 compared with 24% of those on placebo [66], which sits favourably alongside response rates from TNFi therapies. Secukinumab has also been shown on MRI to reduce spinal inflammation as early as week 6 in patients with AS [67]. A small observational study has shown that these MRI findings are sustained over time, with 87% of baseline vertebral corner inflammatory lesions having resolved at 2 years in patients who received secukinumab continuously [67]. Further evidence from two larger phase 3 studies (MEASURE 1 and MEASURE 2) showed significant reductions in disease activity in patients with AS [68], leading to the current licence for secukinumab. MEASURE 1 also showed a low overall rate of spinal radiographic changes at 2 years [69]. However, longer-term controlled studies are needed before definite conclusions can be made as to whether anti-IL-17 therapy is effective in inhibiting radiographic progression.

Finally, recent data from phase 3 studies with secukinumab have shown the effectiveness of inhibiting IL-17 in patients with radiological SpA who were naive to biologic DMARDs or inadequate responders to TNFi therapy (TNFi-IR) [70, 71]. Of those patients who were TNF naive in the phase 3 MEASURE 2 study, 68.2% who received secukinumab 150 mg achieved ASAS 20 at week 16 compared with 31.1% of those who received placebo (P < 0.001). In the TNFi-IR group, 50.0% of patients treated with secukinumab 150 mg achieved an ASAS 20 response compared with 24.1% of those treated with placebo (P < 0.05) [70].

Both the MEASURE 1 and MEASURE 2 phase 3 studies, discussed in more detail later in this supplement, pave the way for further research and new trials of anti-IL-17 therapies. Ultimately these drugs could provide a valuable therapeutic alternative for patients with AS who respond poorly to NSAIDs and TNFi therapy.

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