Treatment strategies in axial spondyloarthritis: what, when and how?

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Abstract

There have been major advances in the management of axial spondyloarthritis (axSpA) with the introduction of effective biologic agents targeting TNF and IL-17A. Clinicians now have more choice but, despite treatment recommendations, are still faced with significant uncertainty when deciding on the optimal treatment strategy for an individual patient in clinical practice. Management of axSpA typically requires both non-pharmacological and pharmacological interventions. NSAIDs remain the first line drug therapies for axSpA with proven efficacy for symptomatic management but uncertainty remains regarding their optimal long-term use relating to radiographic progression and safety in axSpA. To-date there are no head-to-head trials of biologics in axSpA. Clinicians need to consider other factors, including extra-articular manifestations, comorbidities, safety and radiographic progression when deciding on which biologic to recommend for an individual patient. This article will explore the evidence relating to these factors and highlight areas of unmet need.

Key words: axial spondyloarthritis, AS, treatment, NSAIDs, biologic DMARDs, early treatment, TNF, IL-17

Rheumatology key messages
• There have been major advances resulting in more treatment options for axSpA.
• Extra-articular manifestations and comorbidities can help inform biologic choice in axSpA.
• Early treatment is associated with better clinical response but evidence for reduced radiographic progression is still awaited.

Introduction

There have been major advances in the diagnosis, classification and understanding of the pathophysiology of axial spondyloarthritis (axSpA). This has led to the successful introduction in the clinic of new agents for the treatment of axSpA. However, despite treatment recommendations [1,2], there remain many unanswered questions relating to how best to use existing, and upcoming, therapies to achieve optimal outcomes for patients with axSpA. Here we consider the available therapies in axSpA, highlight specific areas of uncertainty relating to these and present suggestions to support clinical decision making in this setting.

What treatment options do we have in axSpA?

Optimal treatment of axSpA requires a combination of non-pharmacological and pharmacological treatments. Non-pharmacological strategies involve mainly exercise therapies, education, lifestyle and behavioural changes and self-management. The current licensed drug treatments for axSpA are NSAIDs and biologic DMARDs (bDMARDs) targeting TNF or IL-17A, which in general appear to have similar clinical efficacy in AS and non-radiographic axSpA [3–5].

Which patients should receive non-pharmacological treatments and what are the options?

With the current medicalized view of healthcare and all the excitement and publicity about new drugs, it is tempting to focus mainly on pharmacological therapies for axSpA. However, the optimal management of all people with axSpA requires non-pharmacological interventions, with the addition of pharmacological

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SUPPLEMENT

treatments for those with more symptomatic or active disease despite this.

AxSpA sits at the intersection of biomechanics and immunology [6,7], so attention to both aspects is key. Regular exercise and stretching are well established in the management of axSpA [1,2]. Although exercise has lower treatment effects compared with TNF-inhibitors, it remains the cornerstone in the treatment of axSpA. In addition to improving many axSpA outcomes, including disease activity, pain, spinal mobility and function [8,9], regular exercise has significantly lower cost and fewer adverse effects compared with NSAIDs or biologics, with additional benefits for general health and well-being.

The need for regular exercise applies across the axSpA spectrum and throughout the lifespan of the condition. The optimal intensity and format of exercise in axSpA remains unclear, with current evidence favouring a combination of endurance and strength training [9]. It is unlikely that there will be a single exercise regimen suitable for all people with axSpA, so a more personalized approach is required, with the type and intensity of the exercise adapted to the patient's demographics, preferences, comorbidities and disease severity.

Interestingly, the systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for axSpA management noted that, to date, none of the studies of exercise therapy in combination with TNF inhibitors demonstrated any additional benefit on function or spinal mobility in the short-medium term compared with anti-TNF therapy alone [9], although treatment with TNF inhibitors may increase exercise capacity in axSpA [10]. Despite the absence of evidence, clinicians should explicitly highlight to their patients that exercise also applies to those on biologic therapies as there are likely to be additional and longer-term benefits on other aspects of the disease, including comorbidities, as well as on general physical and mental health.

As for all chronic conditions, education is an important component of management and facilitates shared decision-making [11,12]. Smoking cessation is worthy of specific attention in axSpA in light of the association with worse clinical and radiographic outcomes [13–15]. A more detailed review of exercise and non-pharmacological treatment for axSpA is beyond the scope of this paper and readers are referred to the systematic literature review by Regel *et al.* [9].

How should NSAIDs be used in axSpA?

NSAIDs for management of symptoms and inflammation in axSpA

NSAIDs remain the first-line drug treatment, in those without contra-indications, for symptoms in axSpA [1,2]. The efficacy of NSAIDs for axSpA symptoms is established, with no significant differences between specific NSAID agents [9,16]. Similarly, no significant efficacy differences have been reported between patients with AS and non-radiographic axSpA [17]. Naproxen alone led to sustained partial clinical remission in a third of patients with early axSpA [18,19].

In addition to symptomatic improvement, reduction of inflammation is a treatment aim in all inflammatory rheumatic musculoskeletal disorders. MRI results in the INFAST study, in which patients were randomized to receive naproxen (1000 mg/day) plus infliximab or naproxen plus placebo for 28 weeks, indicate that naproxen significantly improved MRI spine and sacroiliac joint osteitis [20]. Not surprisingly, effects were more pronounced in the group also treated with infliximab but the results do suggest direct anti-inflammatory effects of NSAIDs in axSpA. A single-centre cohort study also found a reduction in MRI sacroiliac joint bone marrow oedema signal after 6 weeks of full dose NSAIDs in newly presenting patients with axSpA, although the majority of patients were unable to continue high-dose NSAIDs throughout this period [21]. While these and other data may suggest that NSAIDs ameliorate inflammatory features in the target tissues on MRI in axSpA, neither of these studies included a placebo arm, so contribution of the natural course of the disease on regression of the radiographic findings cannot be excluded.

The risk-benefit ratio of NSAIDs should be carefully considered for each individual when prescribing NSAIDs and should be regularly reviewed in those taking these agents long-term. The long-term cardiovascular safety of NSAIDs remains a concern for many clinicians, particularly in chronic conditions like axSpA. A large population-based study reported that recent (during the prior three months) use of NSAIDs increased the risk for ischaemic heart disease 1.4-fold for traditional NSAIDs and 3.0-fold for COX-2 inhibitors in AS compared with matched controls [22]. However, this does not reflect long-term NSAID use and other confounders, such as AS disease activity, were not included. In contrast, a large retrospective population-based study using administrative data reported that despite an increased background risk of cardiovascular death in patients with AS, this was inversely correlated with NSAIDs [23]. Similarly, Bakland *et al.* [24] found that not using NSAIDs was associated with reduced survival (odds ratio 4.35) in AS patients. Therefore, there is no convincing evidence that NSAIDs increase cardiovascular risk in axSpA on a group level, and they may even have a protective effect, presumably by reducing inflammation and/or facilitating increased physical activity, although cardiovascular risk should be assessed and discussed on a case-by-case basis.

NSAIDs and radiographic progression

While the efficacy of NSAIDs in treating axSpA symptoms is established, there have been conflicting results on the ability of NSAIDs to reduce radiographic progression. Two clinical trials had suggested that continuous

use of NSAIDs in AS was associated with less radiographic progression than on-demand NSAIDs, particularly in those patients with an elevated CRP [25,26]. This was supported by an observational cohort study reporting less radiographic progression with high-dose compared with low-dose NSAIDs, most pronounced in patients with existing radiographic syndesmophytes and elevated CRP [27].

However, a subsequent randomized trial of continuous *vs* on-demand diclofenac failed to demonstrate significant difference in radiographic progression at two years [28] and a recent meta-analysis reported no significant difference in radiographic progression between AS patients treated with NSAIDs compared with no NSAIDs, high *vs* low NSAID-index or continuous *vs* on-demand NSAIDs [29]. As a result of the uncertainty and the potential toxicity of continuous/high dose NSAIDs, the latest ASAS/EULAR treatment recommendations suggest that the decision to use continuous NSAIDs should be based on symptomatic response, rather than considerations about the possibility of a protective effect on radiographic progression [1], while the recently updated ACR/SPARTAN treatment recommendations maintained support for continuous use of NSAIDs [2].

Therefore, while the role of NSAIDs in the symptomatic management of axSpA is established and NSAIDs appear to reduce inflammatory changes on MRI, uncertainty remains regarding the optimal long-term dose and frequency. Better stratification may help identify those most likely to benefit from continuous high-dose NSAIDs and to justify the potential increased risks associated with this. However, even if high-dose continuous use were desirable and recommended, the reality is that up to one-third of patients cannot tolerate the maximum doses of NSAIDs and only a minority will comply with this [17,21], while a significant number will not obtain sufficient symptomatic response, necessitating escalation of therapy.

Biologic DMARDs in axSpA

Biologic cytokine inhibitors are by far the most effective currently available treatments across the axSpA spectrum. TNF inhibitors are firmly established in the management of patients with active, moderate-severe axSpA and have been joined in the clinic by drugs targeting IL-17A [30–33]. The efficacy of TNF and IL-17A inhibition in axSpA are consistent with the compelling evidence for the central role of the IL-23/IL-17 pathway in spondyloarthritis (SpA) pathogenesis [34]. It was therefore widely anticipated that inhibition of IL-23 would be similarly successful in axSpA. However, inhibition of both IL-12/IL-23p40 with ustekinumab and IL-23p19 with risankizumab failed to reach their primary and major secondary endpoints in axSpA [35,36]. These, at the time unexpected, results challenge our existing understanding of IL-23/IL-17 and highlight the importance of performing robust phase 3 randomized-controlled trials (RCTs), even in the face of compelling pre-clinical data

and promising early phase studies, and of publishing negative trial results. The exact reasons for the failure of IL-23 inhibition in axSpA remain unclear, with IL-23-independent production of IL-17 and/or tissue-specific differences proposed as possible explanations [37,38]. Intriguingly, data from an inducible HLA-B27/Huβ2m transgenic rat model of SpA suggests that inhibition of IL-23 may protect against the development of experimental SpA but not ameliorate this once disease is established, whereas inhibition of IL-17A was effective both prophylactically and in established disease [39,40].

Despite the positive results with TNF and IL-17A inhibitors, the response rates remain far below the high hurdle responses seen with newer biologics in psoriasis, indicating the need for both a better understanding of tissue-specific pathophysiology and for additional therapies for axSpA. JAK inhibitors are a promising therapeutic modality for axSpA, with several phase 3 clinical trials underway. Their exact mechanism in axSpA is still not entirely clear but is likely to involve the IL-23/IL-17 axis in which several key cytokines exert their function via the JAK-STAT pathway [41]. The pan-JAK inhibitor tofacitinib and the JAK1 inhibitors filgotinib and upadacitinib have all reported promising phase 2 results in AS [42–44], with phase 3 results awaited. A number of other novel therapeutic options are in various stages of development for axSpA, including anti-cytokine agents targeting other components of the IL-17 superfamily and different pathways, and small molecule agents targeting transcription factors, intracellular signalling and epigenetic modification [45].

Can we predict which patients are most likely to respond to biologic therapies in axSpA?

When prescribing a biologic therapy in axSpA, clinicians should always consider the likelihood of the patient responding to the available biologics. Several factors, some of them modifiable, have been identified as predictors of response to treatment with bDMARDs in axSpA. Observational data indicate that, generally, HLA-B27 positivity, younger age, shorter disease duration, male gender, elevated CRP and inflammatory MRI features are associated with higher response rates to TNF inhibitors in axSpA, while obesity and smoking are associated with lower response rates [46–54]. These factors are not entirely surprising; the predictors of 'good response' essentially reflect a higher likelihood of the patient truly having active inflammatory axSpA, as opposed to other causes of back pain. Therefore, careful clinical assessment and consideration prior to commencing biologics and, again in those who fail to respond to a particular bDMARD, is a crucial part of decision making. Simply applying classification criteria and following treatment guidance using a pre-defined checklist or algorithm approach is not appropriate for clinical practice; the latter requires thoughtful exclusion of other potential causes (such as degenerative disc disease, fibromyalgia) for the patient's symptoms, which are unlikely to respond to biologics and which require different

TABLE 1 Efficacy of cytokine and JAK inhibitors across the spondyloarthritis spectrum

Condition	Drug class				
	Monoclonal TNF inhibitors	Etanercept	IL-17A inhibitors	IL-23p19/p40 inhibitors	JAK inhibitors
AxSpA	++	++	++	−−	(+)
Uveitis	++	(+)	?	?	?
IBD	++	−−	−−	++	CD (?/+) UC ++
Psoriasis	++	++	+++	+++	(+/++)
Hidradenitis suppurativa	++[a]	(+)	(+)	(+)	?

[a]Only adalimumab licensed.

+++: proven efficacy with high level responses; ++: proven efficacy; +: limited efficacy/limited evidence of efficacy; −: no efficacy; ?: no evidence; (): not licensed; AxSpA: axial spondyloarthritis; CD: Crohn's disease; UC: ulcerative colitis.

management strategies. Smoking and obesity are recognized associations with poor response to biologics across the immune mediated inflammatory disease spectrum, so should be actively addressed as part of optimal clinical management. It remains to be seen whether the same predictors apply for drugs targeting IL-17 or JAKs but it seems likely these will remain valid for the reasons outlined.

How can we decide which bDMARD is likely to be the best choice for an individual patient?

There are, to date, no validated biomarkers or head-to-head RCTs of biologics in axSpA to guide choice of biologic agent in axSpA. While there are now two head-to-head studies of a TNF inhibitor vs an IL-17A inhibitor in psoriatic arthritis [55,56], any differences appear to be driven mainly by cutaneous disease, consistent with the results in the psoriasis RCTs, so these results are of limited relevance to axial disease in axSpA. On a group level, there do not appear to be any major differences in the efficacy of various TNF inhibitors for axSpA itself [57], although there are clearly differences on an individual patient level, which remain poorly understood and poorly studied in axSpA. Clinicians therefore need to carefully consider other factors, including the presence of extra-articular manifestations (EAMs) and comorbidities, the risk of radiographic progression and safety when making treatment decisions.

Can EAMs inform choice of biologic in axSpA?

In addition to the musculoskeletal components that form the primary endpoints of RCTs, axSpA is associated with characteristic EAMs including IBD, psoriasis and uveitis [4]. These EAMs have differential responses to biologics, so offer an opportunity to inform treatment decisions in axSpA (Table 1). However, data for these EAMs are generally in the form of secondary outputs from axSpA RCTs, open-label prospective or observational studies or from the primary conditions themselves.

For uveitis, monoclonal TNF inhibitors are more effective than etanercept. Data from the Swedish biologics registry and from a US claims database reported that adalimumab and infliximab are associated with reduced risk of acute anterior uveitis development and flares in patients with AS, compared with etanercept [58,59]. Data for golimumab and certolizumab are also suggestive of efficacy for uveitis in axSpA [60,61]. There are currently very limited data available for IL-17A and JAK inhibitors in uveitis, with secukinumab failing to meet the primary efficacy endpoints in three small linked RCTs of non-infectious uveitis [62]. Therefore, at this stage, the existing literature would support the preferential use of monoclonal TNF inhibitors, and their biosimilar versions, in patients with active axSpA who require a bDMARD and who have frequent or refractory anterior uveitis, although none of the other licensed biologics for axSpA appear to be contra-indicated in the presence of uveitis.

IBD is another frequently reported EAM in axSpA. There are clear differences in efficacy in IBD between TNF inhibitors, with several monoclonal antibody TNF inhibitors effective and licensed for IBD, but not the soluble-fusion protein etanercept [63–65]. Despite promising pre-clinical data in IBD, inhibition of IL-17 with secukinumab and brodalumab was associated with worsening Crohn's disease [66,67]. Reassuringly, the incidence of new-onset IBD with IL-17A inhibition appears uncommon in axSpA and psoriasis [68,69]. While inhibition of IL-23 appears to be an effective strategy in IBD [70], this is not effective for axSpA [35,36]. Vedolizumab, an α4β7 integrin blocker licensed for the treatment of IBD [71], has been reported to precipitate enthesitis and sacroiliitis in some patients [72], so should be used with caution in patients with IBD and axSpA. The results for the JAK inhibitors in IBD have been more mixed, with tofacitinib failing to reach its primary end point in Crohn's disease but effective in ulcerative colitis, while the JAK1 inhibitors filgotinib and upadacitinib have reported promising early-phase results [73,74]. The efficacy of these molecules for IBD encountered in the setting of axSpA remains to be defined. Therefore, in patients with axSpA and IBD, monoclonal TNF inhibitors

currently appear to be a logical first choice biologic. However, the best biologic choice in patients with both axSpA and IBD who fail or who are intolerant of TNF inhibitors is not currently clear in light of the divergent results with inhibition of IL-17 and IL-23; in future, there may be a role for the newer JAK inhibitors here if their efficacy and safety for both primary conditions is confirmed in phase 3 studies.

In contrast, in psoriasis, the dominance of IL-23/IL-17 inhibition over TNF inhibition has been firmly established in head-to-head studies, with transformative high-hurdle cutaneous responses [75]. Therefore, in patients with active axSpA and severe psoriasis, IL-17A inhibitors would be a logical choice as first biologic, with TNF inhibitors as alternative agents.

Hidradenitis suppurativa is more commonly reported in patients with axSpA compared with the general population [76], while patients with hidradenitis suppurativa are at increased risk of developing AS [77]. Adalimumab has been approved for the treatment of hidradenitis suppurativa, while infliximab and drugs targeting IL-17 also appear to be promising therapeutic options [78].

Many patients with axSpA also have more than one EAM, further complicating treatment decisions due to divergent responses in different tissues (Table 1). Therefore, clinicians managing patients with axSpA require knowledge of the immunopathology of conditions across the SpA spectrum.

In addition to EAMs, other comorbidities have implications for safety and should also be considered when choosing a biologic agent in axSpA. Therefore, while efficacy in axSpA, and associated EAMs, are usually the primary factors informing biologic choice in a particular patient, safety related to EAMs and comorbidities also needs to be carefully considered, particularly as other therapies with alternative mechanisms of action become available, leading to increased choice in terms of both efficacy and safety profiles.

Should radiographic progression be a consideration for choice of biologics in axSpA?

The concept of preventing radiographic progression is well established in RA and, with the advent of effective biologic therapies, has also entered the axSpA field. When radiographic changes occur in axSpA, the progression appears to be largely linear over time in the early stages of the disease [79]. However, unlike RA where the majority of patients, particularly those who are seropositive, are 'at risk' of developing permanent structural damage (i.e. erosions) as part of the natural history of RA, radiographic progression in axSpA is heterogeneous, with a significant number of patients never developing any radiographic changes. Furthermore, in those that do develop radiographic changes, this process is far slower than RA, making the impact of interventions on structural changes more difficult to assess and monitor.

While initial studies suggested ongoing radiographic progression in axSpA at two years despite treatment with TNF inhibitors [80,81], reduced structural changes with TNF inhibitors were subsequently reported with longer follow-up and in a prospective study [29,82–84]. Extension of the MEASURE1 study indicates that the majority of patients with AS treated with secukinumab had no radiographic progression over 4 years [85]. Both TNF and IL-17A inhibitors have been shown to reduce inflammatory changes on MRI scans [86–89] and, as disease activity is associated with radiographic progression [84,90], the current paradigm is that reducing inflammation will ultimately lead to reduced radiographic changes. Robust long-term head-to-head studies will be required to determine whether inhibiting certain biologic targets and pathways is more effective than others at inhibiting radiographic progression, but in the absence of clear evidence, the current target of therapy with bDMARDs in axSpA should be good control of symptoms and inflammatory features. It remains to be determined whether clinical remission or low disease activity targets will translate into more effective retardation of radiographic progression in axSpA to warrant a more aggressive treat-to-target approach. Even if this were the case, it is not clear how this would be achieved as only a small proportion of patients achieve ASDAS inactive disease with the currently available biologics [91,92].

Whether bDMARDs and NSAIDs have a synergistic effect on clinical outcomes and slowing of radiographic progression in axSpA remains unclear. There are no studies directly addressing this question, with no major differences noted between continuing or reducing NSAIDs in patients on biologics (for example, the similar outcomes in the SPARSE and SPINE etanercept studies [93,94]).

Importantly, as treatment response needs to be assessed promptly and radiographic progression is a long-term target with a very heterogeneous natural history, predictors of radiographic progression may be helpful in identifying subgroups of patients that warrant more intense and earlier treatment. Data from large cohort studies have suggested that higher disease activity, including CRP, is associated with radiographic damage, making this a good short-term surrogate marker and target [84,90,95,96]. Other factors reported to be associated with radiographic progression include HLA-B27 positivity, the presence of baseline syndesmophytes, male gender, physically demanding jobs, smoking and socioeconomic status [15,96,97].

Therefore, inhibition of structural progression is not currently a useful treatment guide or target in the majority of patients with axSpA during therapeutic decision-making beyond clinical outcome measures of disease activity, although clearly this should be a consideration in those at risk of radiographic progression.

What other factors can help in choosing biologics in axSpA?

Clinical efficacy and safety should be the primary treatment considerations for delivering 'best care' in all cases.

Nevertheless, biologics remain high-cost therapies, so cost is often also a relevant consideration, particularly in resource-limited healthcare settings. There are a number of reviews comparing the relative costs of biologics in axSpA [98,99]; however, these cannot easily be extrapolated due to significant differences in healthcare funding, reimbursement and costs of biologics between, and often within, countries. Furthermore, the introduction of biosimilars has led to a significant drop in the cost of treatment and downward pressure on the costs of existing biologics in some but not other countries [100]. These issues therefore need to be considered in the context of the local situation. The EULAR treatment recommendations include an overarching principle that costs can drive the choice between treatments only if the outcome is expected to be similar under either treatment (i.e. the primary driver should be clinical) [1].

What about timing? Does early treatment lead to better results?

The paradigm from RA that early treatment is associated with better treatment response and improvement in function and imaging findings is generally also accepted for axSpA [101]. 'Early' could refer to duration of symptoms or to imaging/laboratory findings. However, is there really a 'window of opportunity' in axSpA as for RA?

While there are few studies directly testing the impact of early *vs* later therapy, or treat-to-target strategies, in axSpA, there is increasing evidence that shorter disease duration is associated with better response to NSAIDs and TNF inhibitors [18,52,96]. In the INFAST study of biologic-naïve patients with active axSpA with disease duration ≤3 years, ASAS partial remission at week 28 was achieved by 62% and 35% of the patients in the naproxen plus infliximab and naproxen plus placebo groups, respectively [18], which was largely maintained until week 52 [19]. Response to NSAIDs in this study is significantly higher compared with other studies that had no restriction on disease duration [102]. While caution should be applied when comparing results between different studies, there are now several studies that have reported high response rates with TNF inhibitors in patients with short symptom duration [18,52,96,103–105], in excess of those seen in the original phase 3 RCTs in patients with much longer disease duration [106–108]. Unfortunately, while tapering may be an option in some patients with sustained remission, the current data suggests that stopping bDMARDs is not a viable option, nor recommended, for the majority of patients [1,3].

Evidence that early treatment *per se* leads to reduced radiographic progression in axSpA is still awaited, although there is some indirect evidence suggesting that early control of inflammation (CRP and/or MRI) is associated with better radiographic outcomes [96,97,109–111]. The issues with assessing radiographic progression in axSpA have been outlined previously and are particularly relevant to non-radiographic axSpA as these patients tend to have lower CRP levels and less evidence of axial inflammation on MRI [112].

In summary, while early intervention is an appealing and increasingly promoted concept in inflammatory rheumatic diseases, there is, to date, no high-level evidence that early intervention with biologics leads to better radiographic outcomes in axSpA, so dedicated studies are required to assess this.

Conclusions

Despite significant advances in the management of axSpA, and treatment guidelines that provide a framework, clinicians continue to face many uncertainties about the best treatment options for an individual patient. Clinicians need to consider multiple components in decision-making and need to have a working knowledge of immunopathology and therapy across the SpA spectrum. This situation will be amplified when new agents with other mechanisms of action become available for axSpA. In order to translate these advances into significant additional improvements in patient outcomes, further research is required, including carefully designed head-to-head studies and research in subgroups at high risk of radiographic progression and long-term disability.

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