Axial Spondyloarthritis in the Era of Precision Medicine

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KEYWORDS

• Spondyloarthritis • Ankylosing spondylitis • Anterior uveitis
• Extra-articular manifestations

KEY POINTS

- In axial spondyloarthritis (axSpA), when a biologic is required, guidelines still recommend to initiate with a tumor necrosis factor-α inhibitor (TNFi), based on long-term experience.
- Extra-articular manifestations (EAMs), such as anterior uveitis, psoriasis, and inflammatory bowel disease (IBD), are common in axSpA
- TNFi generally have a beneficial effect on EAMs, although this might not apply to the effect of etanercept on uveitis or IBD.
- IL-17a are effective in psoriasis treatment, but evidence on uveitis or IBD is contradictory and limited.

AXIAL SPONDYLOARTHRITIS

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that predominantly manifests in the spine, but can also cause peripheral symptoms, such as enthesitis, peripheral arthritis, or dactylitis. axSpA is classified as radiographic axSpA, with radiographic signs of sacroiliitis, or nonradiographic axSpA, with presence of HLA-B27, clinical SpA characteristics, and/or inflammation of the sacroiliac joints at MRI.[1]

Aside from spinal and articular symptoms, many patients with axSpA suffer from extra-articular manifestations (EAMs), such as anterior uveitis (25%–30%), psoriasis (10%–25%), and inflammatory bowel disease (IBD; 5%–10%).[2–4] These EAMs are considered to be equally prevalent in radiographic and nonradiographic axSpA, although some evidence suggests anterior uveitis to be slightly more common in radiographic axSpA.[2] Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biologics may have different effects on these EAMs. This should be taken into account when choosing the right option for therapy. This paper first gives an overview of the current treatment recommendations in axSpA and subsequently describes the occurrence and treatment preferences in EAMs.

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TREATMENT IN AXIAL SPONDYLOARTHRITIS

Initiation of Treatment

The first step to treat axSpA includes physical therapy and maximum doses of NSAIDs. In addition, this phase includes counseling on the negative effects of smoking and overweight, and the importance of exercise. Patients can respond differently to the different NSAIDs, both regarding efficacy and side effects, although studies do not suggest the preference of one NSAID over another.[5] The use of NSAIDs is contraindicated in patients with IBD. Although the efficacy of DMARDs at the axial manifestations has been disappointing in axSpA, in case of prominent peripheral arthritis, or unavailability of biologics, sulfasalazine or methotrexate could be considered.[6]

If at least two different NSAIDs give an insufficient decrease in disease activity (persistent Ankylosing Spondylitis Disease Activity Score $\geq$2.1 or Bath Ankylosing Spondylitis Functional Index $\geq$4), after at least 3 to 6 months of treatment, the addition of a tumor necrosis factor-α inhibitor (TNFi) is indicated. Several randomized placebo-controlled trials have shown a substantial improvement in disease activity in 60% to 70% of patients for adalimumab, certolizumab, etanercept, golimumab, and infliximab.[7] More recently, interleukin (IL)-17a inhibitors (secukinumab and ixekizumab) have become available for the treatment of axSpA.[6,8] Although head-to-head trials are unavailable, indirect comparison of TNFi and IL-17a shows comparable results.[9] Both the 2016 ASAS-EULAR and 2019 American College of Rheumatology guidelines still recommend to initiate treatment with a TNFi, mostly based on long-term experience with these drugs.[6,10] However, in case of primary nonresponse to TNFi, the guidelines recommend to switch to an IL-17a inhibitor, rather than a second TNFi. Last, IL-23 blockers (eg, ustekinumab) are not effective in axSpA.[11] It is important to note that biologics have been mostly studied in radiographic axSpA, and to a lesser extent in the nonradiographic variant. Some studies suggest that the success rate of TNFi might be slightly lower in the latter, whereas studies on IL-17a inhibitors are still ongoing.

Treatment options for axSpA in general are regarded as safe, if the previously mentioned contraindications for NSAIDs are taken into account. However, concerning biologic agents, TNFi and IL-17a inhibitors induce an increased susceptibility to bacterial infections and could potentially reactivate latent tuberculosis.[12] Therefore, patients treated with biologics might require earlier antibiotic intervention in signs of an infection. In addition, TNFi might be associated with a slightly increased risk of (worsening of) demyelinating diseases or malignancy (mostly of the skin, or potentially lymphoma), although this is rare and evidence is still conflicting (e.g., lymphomas were mostly reported for patients with rheumatoid arthritis, where the disease itself is also associated with an increased risk of lymphoma).[13,14] However, these conditions are considered a relative contraindication to use a TNFi. The evidence on TNFi during pregnancy is limited, but current studies do not suggest an increased risk of adverse pregnancy outcomes. The EULAR recommendations report a safe use of infliximab and adalimumab in the first trimester, and etanercept up to the second trimester,whereas certolizumab can be used throughout the entire pregnancy.[15] The use of IL-17a inhibitors during pregnancy is discouraged because studies in humans are lacking.

Reduction of Treatment

It is still unclear how long TNFi should be continued once remission is achieved. Currently, international treatment guidelines recommend to taper the use of a TNFi in case of sustained low disease activity, to avoid unnecessary overtreatment.[10] A few, mostly small, studies have shown that it is possible to maintain a low disease activity when the use of the TNFi is tapered, wherein reduction of the dose shows better

results than discontinuation.[16,17] A recent, noninferiority study has shown that reducing the dose of TNFi by one-third was not inferior to maintaining the standard dose.[18] However, aside from the latter, tapering has been studied limitedly in axSpA, with small patient numbers, mostly retrospective designs and with different tapering protocols.[17] Importantly, there is still a lack of a standardized tapering strategy regarding the best method (dose reduction versus extension of the dosing interval, either at once or gradually) and level of reduction (most studies described a 30%–50% reduction). From a practical point of view, extension of the dose interval would be preferred because it does not require changes of the commercially available injections and is more patient friendly. From both a cost-effective and patient-friendly perspective, in the future, ideally, every patient should receive just as much TNFi as necessary to achieve and maintain treatment effect. Therefore, some studies have evaluated the association between TNFi drug levels and treatment efficacy, attempting to define the optimal cutoff values for TNFi levels. However, although studies in other rheumatic diseases were hopeful, unfortunately in axSpA the evidence for using TNFi levels as a guidance during treatment is still contradictory.[19–21]

EXTRA-ARTICULAR MANIFESTATIONS IN AXIAL SPONDYLOARTHRITIS AND CHOICE OF TREATMENT

Acute Anterior Uveitis

Acute anterior uveitis (AAU) is an acute inflammation of the anterior part of the uvea, involving the iris, ciliary body, and anterior chamber of the eye. Anterior uveitis, just as axSpA, is strongly associated with the HLA-B27 gene, although HLA-B27-negative patients can develop AAU as well. In the general population, the lifetime cumulative incidence is 0.2%, and this is increased to 1.0% in HLA-B27-positive persons.[22] In axSpA, the estimated AAU flare rate is 15 per 100 patient years (TNFi-naive population), with a lifetime risk of approximately 30%, increasing with disease duration.[23,24] Importantly, AAU can be the first presenting symptom of axSpA. In fact, previous studies estimated a prevalence of no less than 40% to 50% of previously undetected axSpA in patients presenting with AAU.[25–28] Because early treatment of axSpA can enhance the prognosis, it is essential that ophthalmologists pay close attention to the presence of back complaints in patients with AAU.

AAU generally occurs in acute unilateral attacks (90%), and is recurrent in 50% of the patients, alternating between eyes. Patients suffer from severe ocular pain, redness of the eye, photophobia, and blurred vision. In up to 20% of the patients, AAU causes complications, such as posterior synechiae (resulting in an irregular pupil), cataract, or glaucoma.[29] AAU generally responds well to local treatment with corticosteroids and mydriatics, and only rarely additional treatment with periocular or oral corticosteroids is indicated. Timely treatment can reduce the risk of complications and if treated adequately, AAU normally resolves within 3 months. Therefore, in patients with axSpA with ocular complains, immediate referral to the ophthalmologist is recommended.

Because AAU has a good long-term prognosis, and flares respond well to local treatment, AAU is in most cases not an indication for preventive (chronic) treatment. However, AAU is invalidating and importantly influences the patient's quality of life. Therefore axSpA treatment should, preferably, also have beneficial effects on the occurrence of AAU.[30] Unfortunately, the first treatment step in axSpA, NSAIDs, are not effective in the treatment or prevention of AAU, although one recent study suggested that the addition of NSAIDs to TNFi treatment might be beneficial.[31] A limited number of retrospective studies suggest a beneficial effect of sulfasalazine and

methotrexate in the prevention of HLA-B27-positive AAU.[32–34] However, methotrexate is not effective in the treatment of the axial manifestations of axSpA, and the influence of sulfasalazine is only limited. Therefore, these DMARDs are not part of the standard axSpA treatment.

Fortunately, TNFi, that are effective in the treatment of active axSpA are also effective in the prevention of AAU. Both infliximab and adalimumab have been widely proven to reduce the risk of an AAU flare and recent studies also show beneficial effects for golimumab and certolizumab.[24,35–39] In general, a 40% to 80% reduction in AAU flares per 100 patient-years is reported during TNFi treatment, compared with placebo or the pretreatment period.[24,35–40] Regarding adalimumab, a prospective study in patients with ankylosing spondylitis with a recent history of AAU, and a subanalysis of a multinational clinical study showed an AAU flare reduction of, respectively, 80% and 51% (and 68% in patients with a recent AAU history) during adalimumab.[36,37] Pooled data from several prospective studies in patients treated with infliximab showed a 79% reduction in AAU flares during treatment.[24] Also for certolizumab, a post hoc analysis of a placebo-controlled trial in axSpA suggested 70% fewer AAU flares during certolizumab, compared with placebo.[38] In addition, recently, a prospective study in patients with axSpA with a recent history of AAU has shown an 87% reduction in uveitis flares during 48 weeks of certolizumab treatment.[41] Last, a prospective study on the occurrence of AAU in patients with axSpA during golimumab reported an 80% decrease in AAU flares, compared with the period before TNFi treatment.[39] Studies on the fusion protein etanercept have been contradictory, with some studies suggesting that etanercept might increase the risk of AAU, instead of preventing it.[42,43] However, a comparison of three randomized studies with etanercept in radiographic axSpA still found a lower frequency of AAU flares in comparison with placebo.[44] Unfortunately, adequate comparison of studies remains a challenge because most trials assessed AAU as a secondary outcome and prospective studies mostly focused on one TNFi and had different designs. Nevertheless, a recent study of the Swedish biologic registry has showed a significantly higher AAU rate in etanercept, compared with adalimumab and infliximab (hazard ratio of 3.86 and 1.99, respectively), which suggests etanercept to be slightly less effective in the prevention of AAU, in comparison with other TNFi.[35] In summary, based on current evidence, AAU cannot be regarded a contraindication for the use of etanercept. However, in patients with highly recurrent AAU, a monoclonal antibody is preferred over etanercept.

Lastly, the IL-17a blocker secukinumab was not efficacious in the treatment of other forms of uveitis in three placebo-controlled phase 3 studies.[45] However, its influence on AAU in axSpA still has to be determined, which also applies to ixekizumab and the IL-23 inhibitor ustekinumab.

In conclusion, AAU is the most common EAM in axSpA. Collaboration with an ophthalmologist is important, to improve early recognition of axSpA and to optimize treatment of patients with axSpA with recurrent AAU. In most cases, AAU attacks respond well to local treatment by the ophthalmologist and in most cases there is no indication for preventative treatment of AAU alone. However, TNFi is successful in the reduction of AAU flares in axSpA, with most evidence for the efficacy of adalimumab, infliximab, certolizumab, and golimumab. Therefore, in patients with recurrent AAU and a high axSpA disease activity, requiring a TNFi, a monoclonal antibody is preferred over etanercept (**Table 1**).

Psoriasis

Psoriasis is a rather common skin disease, occurring in up to 11% of adults and resulting in several types of erythematous plaque lesions with silver scale and nail

Table 1
Efficacy of biologics on extra-articular manifestations in axial spondyloarthritis

		Axial SpA	Anterior Uveitis	Psoriasis	Ulcerative Colitis	Crohn Disease
TNF inhibitors	Infliximab	+	+	+	+	+
	Adalimumab	+	+	+	+	+
	Etanercept	+	±	+	-	-
	Golimumab	+	+	+	+	?[a]
	Certolizumab	+	+	+	?[a]	+
Anti-IL-23	Ustekinumab	-	?	+	?	+
Anti-IL-17	Secukinumab	+	-/?	+	-	-
	Ixekizumab	+	?	+	-	-

Abbreviations: +, beneficial effect; ±, uncertain effect; -, no or negative effect; ?, no data available.
[a] Not approved for this indication.

deformities.[46] Multiple Human Leukocyte Antigen types have been connected to the development of psoriasis, and 40% of patients have a first-degree family member with a psoriatic disorder.[47,48]

Approximately 14% to 20% of patients with psoriasis develop arthritis, which occurs more often in European and North and South American patients.[49] Five percent also suffer from axial symptoms, such as sacroiliitis, although the level of radiographic changes is considered to be less severe and more asymmetrical in psoriatic arthritis compared with radiographic axSpA.[50–52] Conversely, of the patients with axSpA (psoriatic arthritis excluded), 5% to 10% develop psoriasis.[2,3]

The skin manifestations of psoriasis generally respond well to topical corticosteroids or psoralen and ultraviolet A light therapy. In case of moderate to severe skin lesions, systemic therapy is indicated, such as methotrexate, apremilast, or biologic agents (TNFi, anti-IL-12/IL-23, anti-IL-17, and anti-IL-23/IL-39).[53,54] Peripheral joint involvement generally responds well to NSAIDs; intra-articular corticosteroid injections (a combination of); DMARDs (methotrexate, leflunomide); and, in case of insufficient response, to biologics.[55]

Contradictory, in patients treated with TNFi, psoriatic lesions of the skin can occur, such as an exacerbation of existing psoriasis, or a new onset of psoriasis, particularly palmoplantar pustulosis. This paradoxic reaction during treatment has been reported for several disease entities (SpA, psoriatic arthritis, rheumatoid arthritis, and juvenile idiopathic arthritis) and for different TNFi. For example, registry data of adalimumab trials in several rheumatic diseases showed an incidence rate of new onset or worsening of psoriasis in less than 0.1/100 patient years,[56] whereas other studies in SpA, Crohn disease (CD), and rheumatoid arthritis reported a prevalence of 1.5% to 6.4% (infliximab, adalimumab, certolizumab, etanercept).[47,57–62] Some studies reported an improvement after switching to another TNFi, whereas others found reoccurrence, suggesting a class effect.[58,61,63] Overall, in general TNFi is effective in the treatment of psoriasis, psoriatic arthritis, and axSpA. However, in patients developing new or worsening psoriasis after the initiation of TNFi, a potential paradoxic reaction should be considered (see **Table 1**).

Inflammatory Bowel Disease

IBDs, including ulcerative colitis (UC) and CD, are primarily treated by the gastroenterologist. Approximately 4% to 10% of patients with axSpA develop IBD, with a recent meta-analysis describing a pooled-prevalence of 4.1% in radiographic and 6.4% in

nonradiographic axSpA.[2,3] This highest risk seems to be in the first years after axSpA diagnosis.[64] In addition, approximately 40% to 60% of the patients with SpA have asymptomatic microscopic gut inflammation (of whom two-thirds also have macroscopic lesions), according to ileocolonoscopy studies in patients with SpA without gastrointestinal symptoms.[65,66] One study identified a higher axSpA disease activity, male sex, and less spinal mobility to be associated with these gastrointestinal lesions.[65] Up to 6% to 7% of the patients with chronic gut inflammation develop CD.[67,68] Conversely, of the patients with IBD, up to 20% have asymptomatic sacroiliitis, and 40% suffer from clinical articular symptoms, such as inflammatory back pain, arthritis, and enthesopathy.[69,70] Of the patients with IBD, 10% to 15% and 30% eventually develop, respectively, axSpA and peripheral symptoms within 20 years after diagnosis.[71,72]

In patients with axSpA and IBD, it is recommended to discuss the treatment options with the gastroenterologist, because some axSpA treatments might be less effective for IBD. The use of NSAIDs should be minimized in this group, because NSAIDs can worsen bowel inflammation or increase the risk of IBD complications, although selective cyclooxygenase-2 inhibitors might be safe.[73,74] Although DMARDs are generally not effective in the treatment of axSpA, sulfasalazine has shown some positive effects, in particular on peripheral manifestations, and is also known to reduce inflammatory activity in IBD.[75]

In general, in patients with axSpA and IBD, TNFi are recommended over other biologics. In the treatment of IBD, infliximab, adalimumab, and certolizumab are approved for treatment of CD, whereas infliximab, adalimumab, and golimumab are indicated in UC.[6] Etanercept is not approved for IBD and studies show an increased risk of IBD exacerbations in patients treated with etanercept, compared with infliximab and adalimumab.[76,77] The IL-23 inhibitor ustekinumab has proven to be effective in the treatment of IBD, but is not effective in the treatment of axSpA symptoms.[11] Limited evidence on IL-17a inhibitors (secukinumab, ixekizumab) shows low efficacy on IBD, and suggests that the risk of an exacerbation or new-onset IBD might even be increased (although the pooled prevalence in an analysis of seven trials was still <1%) (see **Table 1**).[78,79] Although a direct comparison between TNFi and IL-17a-inhibitors was not performed, the ASAS-EULAR and American College of Rheumatology guidelines recommend the use of TNF inhibitors in patients with axSpA with IBD.[6,10]

SUMMARY

In axSpA, the first treatment step is an NSAID combined with physical exercises, and if insufficient, a biologic is added within 3 to 6 months. Currently, most experience is obtained with TNFi, all of which have approximately the same efficacy in the treatment of axSpA symptoms. In case of (primary) nonresponse to a TNFi, medication should be switched to preferably an IL-17a inhibitor (secukinumab and ixekizumab), or second TNFi. In patients who have achieved a sustained low disease activity, TNFi tapering is considered, where dose reduction is preferred over drug discontinuation. Unfortunately, standardized tapering schedules are lacking.

Many patients with axSpA suffer from EAMs (anterior uveitis, psoriasis, and IBD), of which uveitis (AAU) is the most common one. In patients with axSpA and EAMs, the effect of axSpA treatment on these EAMs should be taken into account when choosing the appropriate therapy. Overall, most TNFi are efficacious in treating the spinal and extra-articular symptoms, but some differences exist. Importantly, etanercept is contraindicated in case of IBD and seems to be less effective in preventing

flares of AAU. In IBD the type of disease (CD or UC) requires different TNFi choices: certolizumab is approved for treatment of CD and golimumab for UC. Until now, IL-17a inhibitors are not recommended in patients with AAU or IBD. Psoriasis generally responds well to all biologics (TNFi, IL-17a inhibitors), but TNFi can induce a paradoxic skin reaction.

Overall, it is recommended that the treatment of axSpA should be individualized, based on the most prominent symptoms and presence of extra-articular and peripheral symptoms.[10]

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest.

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