

Therapeutics for the treatment of spondyloarthritis: what, when and whom

The therapeutic management of ankylosing spondylitis (AS) and spondyloarthritis includes NSAIDs and biological therapies (TNF- α antagonists), as well as nonpharmacological procedures (education and physical therapy). Together with physiotherapy, NSAIDs remain the first-line treatment in AS, especially in patients with axial disease. TNF- α antagonists have been demonstrated to be highly effective in AS, with control of pain, extra-articular manifestations and systemic and spinal MRI inflammation while they are not able to slow down radiographic progression in the spine. Since approximately 20–25% of AS patients are considered as non-major responders to TNF- α blockers, there is an unmet need for alternative therapies.

KEYWORDS: ankylosing spondylitis ■ anti-TNF- α therapy ■ NSAIDs ■ physical therapy ■ spondyloarthritis ■ treatment recommendations

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the role of NSAIDs in the management of ankylosing spondylitis and spondyloarthritis, based on a review
- Describe the role of pharmacological treatments other than NSAIDs, physical therapy, and other nonpharmacological procedures in the management of ankylosing spondylitis and spondyloarthritis, based on a review
- Describe the role of TNF-alpha blocking agents and other biological agents in the management of ankylosing spondylitis and spondyloarthritis, based on a review

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Spondyloarthritis (SpA) refers to an inter-related group of disorders that share a common genetic background and clinical and radiological features. This group is divided into five subtypes including ankylosing spondylitis (AS), which is the major subtype, psoriatic arthritis, inflammatory bowel disease (IBD)-associated arthritis, reactive arthritis and undifferentiated SpA. The most important clinical features of SpA are inflammatory back pain, asymmetrical oligoarthritis predominantly in the lower limbs, enthesitis and dactylitis, and specific extraskeletal manifestations such as psoriasis, uveitis and chronic IBD. Pain, morning stiffness, progressive functional limitation, fatigue and diminished quality of life characterize the clinical patterns of these patients. In addition, cardiovascular comorbidity is a major concern for patients with SpA.

The management of SpA and AS has improved considerably over the past 10 years. For a long time, therapeutics for the treatment of AS were limited to NSAIDs without alternatives, leading to difficulties in the management of patients who are refractory or intolerant to this drug class [1]. TNF- α -blocking agents have led to a dramatic change in this therapeutic approach [2–4]. Radiographic sacroiliitis is required for the diagnosis of AS and for most forms of SpA. It takes between 7 and 10 years for sacroiliac joint changes to be seen on x-rays. New imaging modalities for assessing SpA are now available to accelerate the diagnostic process. Sacroiliac joint or spine MRI is a very helpful method for detecting inflammation on the axial skeleton and thus for early diagnosis. The Assessment in SpondyloArthritis International Society (ASAS) recently developed classification criteria for axial and peripheral SpA [5,6]. For axial SpA, MRI and HLA B27 are two major items that were introduced for the diagnosis. These new criteria facilitate early identification and diagnosis and this may impact the management of patients with short disease duration.

In this review, we concentrate on the different therapeutics available for the treatment of AS and SpA in general, their roles and respective indications and the recommendations for their use. Alternative and emerging drugs are also reviewed. The specific therapeutic management of psoriatic arthritis is not included in this review.

General therapeutic principles for AS & SpA

Short-term and long-term treatment goals for AS and SpA include the control of pain (pain in the spine, the sacroiliac joints and/or the peripheral joints and enthesal structures) and control of stiffness. These treatment goals also include maintaining function, treating and preventing extra-skeletal manifestations, controlling or even stopping radiographic progression, reducing inflammation and allowing the patient to continue working and finally improving quality of life [2–4]. Prevention of cardiovascular complications is another therapeutic preoccupation. Specific recommendations for the management of AS and SpA have been developed by different national or international groups or institutions. The ASAS and EULAR groups have published their own recommendations (FIGURE 1) [7], as have a large panel of experts and practicing rheumatologists (e.g., the Evidence, Experts, Exchange [3E] initiative) [8]. For instance in France, the national recommendations were established by the French Society for Rheumatology [9] and also by the official health authorities [10].

The therapeutic management of AS and SpA must be global and include pharmacological therapies as well as nonpharmacological options with physical treatment, education and surgery. The aims of this treatment are to control disease activity and to prevent flares of the disease, extra-articular manifestations and specific complications, as well as to control inflammation and disease progression, including radiographic progression. One final objective is to enable the

patient to continue as normal with social and professional activities. According to a European and Canadian rheumatologist survey, controlling inflammation is a key goal in the management of patients with AS [10].

NSAIDs: the first-line medication in AS & SpA

■ The NSAID class in the treatment of AS & SpA

NSAIDs are considered to be the cornerstone of medical treatment for AS according to the ASAS group (FIGURE 1). They are recommended by different expert groups and scientific committees (ASAS/EULAR, 3E, French Society of Rheumatology and HAS) [7–9,101] as the first-line treatment to improve pain and stiffness. The level of evidence for the efficacy of NSAIDs in AS is rated 1b in certain placebo-controlled studies (celecoxib) [11]. The rapid symptomatic efficacy of NSAIDs is included in the Amor classification criteria for spondyloarthropathies [12]. Meta-analyses and reviews of the literature on NSAID use in AS (including a review of placebo-controlled trials) have been published [1,13,14]. The therapeutic efficacy is observed within a few days and persists when the treatment is maintained. There is no proof of the superiority of one NSAID over another in AS. Similarly, there are no consistent differences between different doses of NSAIDs and COX-2 selective inhibitors [1,14]. In France, phenylbutazone was considered to be the NSAID of choice for symptomatic treatment of AS, but there are no convincing results showing the superiority of this drug over other NSAIDs and this treatment is no longer on the market [9]. Certain rheumatologists believe that indomethacin is a strong and effective NSAID for the symptomatic treatment of AS, but again, there is no convincing study showing its superiority. Selective anti-COX-2 NSAIDs such as celecoxib and etoricoxib may be used in AS and have been proven to be as efficacious as traditional NSAIDs, and superior to placebo in randomized controlled trials [15,16].

■ When should we give NSAIDs to patients with AS & SpA?

It is recommended to treat patients with NSAIDs during a flare of the disease, after which it is preferable to stop them [9]. A time period ranging from 2 to 4 weeks is generally required to control a flare [8]. In patients with persistently active disease, continuous use of NSAIDs may be required. In this situation, it is recommended

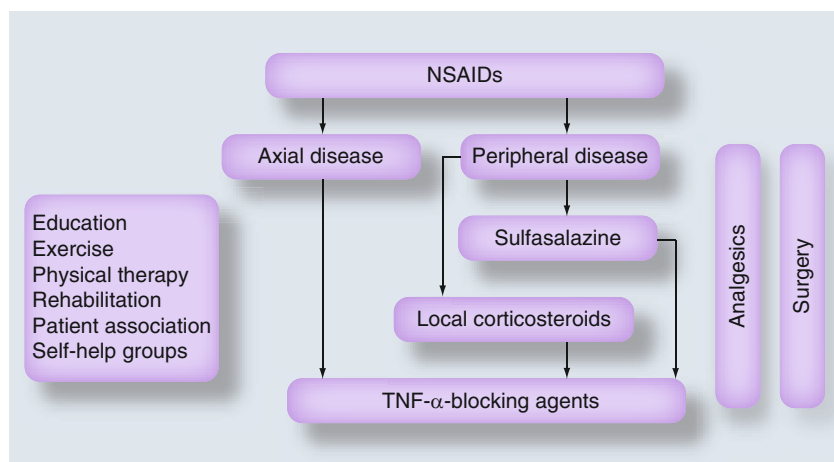


Figure 1. Schematic representation of the recommended management of ankylosing spondylitis according to the Assessment in SpondyloArthritis International Society group. Physiotherapy is the first-line treatment for ankylosing spondylitis and NSAIDs are first-line drugs for ankylosing spondylitis. In patients with peripheral disease, when NSAIDs are ineffective, sulfasalazine should be tested. Another option is corticosteroid joint injections. For patients who do not respond to NSAIDs (patients with axial disease) or corticosteroid injection or sulfasalazine (patients with peripheral arthritis), anti-TNF- α agents may be proposed. Data taken from [7,87].

to give NSAIDs at the lowest dosage possible to control the clinical symptoms, so the minimal effective dosage must be determined first [8,9]. For patients reporting nocturnal symptoms, long-acting NSAIDs should preferably be used. A 2–4 week period with the optimal dosage (or maximum tolerated dosage) is also required to evaluate the effectiveness of NSAID therapy in AS before concluding that the drug is not effective. In this situation, trying another (class of) NSAID is recommended [1,7,9]. The response criteria for NSAID therapy have been established by the ASAS group, but are not used in clinical practice by rheumatologists [17]. NSAIDs are mostly effective on the axial symptoms of AS, but less so on symptoms of peripheral arthritis and especially on dactylitis or enthesitis (TABLE 1) [8].

■ Indications for NSAIDs use in AS & SpA & their safety profile

As stated above, NSAIDs are the first-line medication in the management of patients with AS and SpA. It must be proposed before any other drug, except for patients with a contraindication for their use. In certain situations, NSAIDs must be used with caution. This is the case in patients with concomitant IBD, since NSAIDs are thought to cause a flare of the bowel disease [18]. However, there is limited evidence that NSAIDs can precipitate onset of IBD or flares of pre-existing bowel disease [8]. In light of this statement and according to the clinical

Table 1. Therapeutic options for ankylosing spondylitis and spondyloarthritis and their impact on the clinical manifestations, systemic and MRI inflammation and radiographic progression.

Treatment options	Axial disease	Peripheral disease	Enthesitis/dactylitis	BASDAI/ASDAS	Function (BASFI)	Acute phase reactants	MRI inflammation	Radiographic progression
Physical therapy	+	NS	NS	NS	+	NS	NS	NS
NSAIDs	+	+	±	+	+	NS	-	+
Local corticosteroids	-	+	+	NA	-	NA	NS	NA
Sulfasalazine	-	+	-	+	-	+	NS	NA
Methotrexate	-	-	-	±	±	-	-	NS
Infliximab	++	++	++	++	++	++	++	-
Etanercept	++	++	++	++	++	++	++	-
Adalimumab	++	++	++	++	++	++	++	-
Golimumab	++	++	++	++	++	++	++	-

+: Efficacy; ++: High efficacy; -: Noneffective; ±: Controversial efficacy; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NA: Not applicable; NS: Not studied.

experience of both gastroenterologists and rheumatologists, it is considered that NSAID use in patients with concomitant IBD must be limited and these patients closely monitored by a gastroenterologist [8,9]. The safety of NSAIDs is a major concern and when used appropriately the benefit/risk ratio is favorable, with a rate of serious adverse events of less than 1% per patient-year [2]. However, gastrointestinal, cardiovascular and renal safety issues need to be carefully examined when NSAIDs are administered on a long-term basis [7,8]. The safety profile of NSAIDs does not differ between long and short half-life agents. Higher rates of gastrointestinal complications have been observed with higher dosages and longer durations of NSAID therapy. Selective anti-COX-2 agents are proven to have a better gastrointestinal safety profile, and thus are recommended in patients at higher risk of gastrointestinal side effects [8].

■ NSAIDs & radiographic progression in AS

NSAIDs are effective for pain and morning stiffness, as well as biological parameters of inflammation. By contrast, NSAIDs are considered to have no impact on spinal inflammation as detected by MRI. After 6 weeks of etoricoxib treatment in 15 patients with AS, only a few resolved spinal inflammation on MRI while for most patients, spinal inflammatory lesions worsened or appeared [19]. The role and influence of NSAIDs on the progression of spinal ossification are a subject of debate. This question was examined in a 2-year study including 150 patients with two celecoxib

arms, one receiving continuous treatment and the other on-demand treatment. Progression of spinal ossifications evaluated by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) was lower in the continuous arm compared with the on-demand arm [11]. However, this study was criticized for the very small difference in radiographic progression between the two groups (1.1 point while the mSASSS score ranged from 0 to 74). In addition, it has been established that the minimal pertinent clinical change of the mSASSS score during a 2-year period was 2.7. For these reasons, it has been claimed that there is not enough proof that NSAIDs have a structural effect [9]. However, two recent studies strongly argue in favor of a structural effect of NSAIDs in AS [20,21]. The first was conducted in Germany and included patients with AS and nonradiographic SpA. NSAID intake was calculated during a 2-year period using an index (which takes into account both the dose and duration of drug intake). Patients with AS and a high NSAID intake were characterized by a low likelihood of radiographic progression as evaluated by the mSASSS compared with patients with low NSAID intake. This difference was not observed in patients with nonradiographic SpA [20]. The second study has not been published but was presented at the ACR 2011 meeting [21]. In this study, syndesmophyte progression over 2 years was lower in patients receiving both TNF- α -blocking agents and continuous NSAIDs compared with patients treated with TNF- α blockers alone, although the results were not significant. A *post-hoc* analysis of the trial

comparing continuous and on-demand NSAID treatment [11] gives additional data: in this study, the progression inhibitory effects of continuous use of NSAIDs in comparison with NSAID use on demand was more pronounced in patients with elevated CRP, erythrocyte sedimentation rate (ESR), ASDAS-ESR and ASDAS-CRP [22]. Interestingly, a scoring system for calculating NSAID intake was established by the ASAS group and could be used in clinical trials, such as studies evaluating the structural effect of NSAIDs. This index includes the type of NSAID, the dose and the number of days NSAIDs are taken during a given period [23].

Corticosteroids in the treatment of AS & SpA

■ What & when?

Systemic corticosteroids failed to demonstrate their efficacy in AS, even at a high dosage [1]. Moreover, corticosteroids may precipitate osteoporosis in AS, a complication of the disease. By contrast, a local corticosteroid injection may be the treatment of choice in selected cases, such as resistant enthesitis or refractory sacroiliac pain (FIGURE 1). Local corticosteroid injection in the sacroiliac joints has been evaluated in a controlled trial and showed efficacy compared with placebo [24].

■ For whom?

Corticosteroids can be used in particular clinical situations when the use of NSAIDs are contraindicated, for instance in patients with AS and IBD or during pregnancy or renal failure [8,9].

Role for traditional disease-modifying anti-rheumatic drugs in AS & SpA

■ Traditional drugs in AS & SpA

Traditional disease-modifying anti-rheumatic drugs (DMARDs) that are used in rheumatoid arthritis (RA) have been tested in AS and SpA, especially sulfasalazine (SLZ) and methotrexate (MTX). Sulfasalazine has been evaluated in different placebo-controlled trials, giving mild efficacy in the relief of clinical symptoms of AS. Two meta-analyses examined the efficacy of SLZ versus placebo in AS. The first paper found a beneficial effect of SLZ on morning stiffness, pain and overall wellbeing [25]. The second reported an improvement in morning stiffness and ESR [26]. Interestingly, patients with short disease duration, elevated ESR and peripheral arthritis were more likely to respond to SLZ. Thus, it

is accepted that SLZ must be reserved for AS or SpA patients with peripheral arthritis (FIGURE 1 & TABLE 1) [7–9]. A randomized placebo-controlled trial was recently performed in patients with early undifferentiated SpA with axial disease. This study showed a significant improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in the treatment group compared with the placebo arm [27]. These results may indicate a role for SLZ in patients with early and recent-onset disease, but not in established disease. The recent update of the ASAS/EULAR recommendations for the management of AS confirmed that SLZ had no significant effect on BASDAI and pain in patients with established or long-standing AS [28].

Methotrexate is not very effective in AS. Several open-label trials have been published giving conflicting results (for a review, see [1]). One randomized placebo-controlled trial evaluated the efficacy of MTX in patients with AS, but the primary outcome was a composite index based on seven disease activity measures: morning stiffness, physical wellbeing, BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), Health Assessment Questionnaire (HAQ), and physician and patient overall assessment of disease activity. A responder was defined as an improvement of 20% or more in at least five of the seven variables. At 24 weeks, 53% of patients in the MTX group were classified as responders as compared with 11% in the placebo group [29]. However, the primary criteria chosen had never been previously used or even validated. A meta-analysis by the Cochrane database review system did not find sufficient evidence to support the use of MTX in AS [30]. In addition, in the ASAS/EULAR 2012 updated recommendations for the management of AS, the calculated effect size for MTX did not show any improvement on BASDAI, BASFI, pain or mobility [28].

Leflunomide was ineffective in a randomized placebo-controlled trial in patients with AS, showing no difference in the proportion of ASAS20 responders between the two groups [31]. Thalidomide has been tested in open-label studies in patients with AS and leads to some improvement, but its use is not recommended for AS and related SpA owing to its toxicity [2–4].

■ Indications for traditional DMARDs in the treatment of AS & SpA

The data presented above clearly indicate that there is a limited place for traditional DMARDs in AS and SpA. Their use is not recommended in the treatment of axial manifestations of AS

according to expert opinions. Sulfasalazine may deserve to be considered for AS or SpA patients with concomitant peripheral disease [7].

TNF- α -blocking agents: a major advance in the treatment of AS & SpA

■ Clinical results of the different TNF- α blockers in AS & SpA

TNF- α -blocking agents have been available for approximately 10 years for the treatment of AS and related SpA. They have been proven to be effective in AS during large placebo-controlled studies [32–35] (for a review, see [36]). They are effective for all the different clinical symptoms of the disease, for example, pain in the axial skeleton (spinal and sacroiliac pain), peripheral arthritis and dactylitis and enthesitis (TABLE 1). A recent randomized placebo-controlled trial demonstrated the efficacy of etanercept on refractory and disabling heel enthesitis. Patient's global assessment, heel pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) improved significantly in the etanercept group compared with the placebo arm [37]. In AS and SpA, the response delay to TNF- α -blocking agents was short, with an improvement after 2 weeks. These agents improve morning stiffness, disease activity (evaluated by the BASDAI score) mobility and function (evaluated by the Bath Ankylosing Spondylitis Metrology Index – BASMI – and BASFI score) and also quality of life. According to the ASAS response criteria, they led to ASAS20 response rates between 58 and 61% compared with 19–29% in the placebo group [36]. They also improved pulmonary function [38] and laboratory parameters of inflammation. Four TNF- α blockers are currently available in the treatment of AS: three monoclonal antibodies (infliximab, adalimumab and golimumab) and a p75 soluble receptor (etanercept). Certolizumab, a pegylated Fab anti-TNF- α fragment, is currently used only in RA and studies with this agent in AS and psoriatic arthritis are forthcoming. The different TNF- α blockers gave the same levels of response in the treatment of AS. Since there is no head-to-head trial comparing these drugs, there is no demonstration of the superiority of one agent over another in AS. The number to treat (NNT) to achieve different treatment outcomes is fairly similar between the different TNF- α blockers: for ASAS20, NNTs range between 2.3 and 2.7; for ASAS50, they are between 2.9 and 3.7; for ASAS partial

remission, they are between 4.7 and 5.9 [39]. Choosing between these agents depends on the patient's preference for either subcutaneous injections or intravenous administration, the risk of tuberculosis reactivation (which is higher with the anti-TNF- α monoclonal antibodies), the presence of specific extra-articular manifestations (e.g., uveitis and IBD) and specific comorbidities. The overall research evidence for all TNF- α -blocking agents in AS is high and rated 1b by the ASAS/EULAR groups. The strength of recommendation for the use of all available TNF- α blockers in AS with the recommended dose is rated grade A [39].

■ Recommendations for the initiation of TNF- α -blocking agents in AS & SpA

According to national and international recommendations [40,41], TNF- α -blocking agents are envisaged as a second-line treatment, after conventional treatments such as NSAIDs for patients with axial disease, or SLZ and local corticosteroid injections for patients with peripheral arthritis or enthesitis (FIGURE 1). Failure of two or three NSAIDs (in optimal or recommended dosages, in the absence of contraindications and for a period of 3 months) is defined as an inadequate response to conventional treatment in axial AS according to the French and/or ASAS recommendations [40,41]. Symptoms suggesting severe disease such as hip involvement, recurrent uveitis and severe extra-articular manifestations, may also require anti-TNF- α initiation. The therapeutic response to the TNF- α blocker is evaluated after 6–12 weeks of treatment, with the goal being at least a two point improvement in BASDAI in patients with axial disease and at least a 30% decrease in tender and swollen joint counts in patients with peripheral arthritis. When a patient is considered to be a nonresponder, the clinician may adjust the treatment by increasing the dosage for infliximab or shortening the interval between adalimumab injections or infliximab infusions. However, these therapeutic adjustments have not been validated by health authorities or by specific recommendations. For instance, in a randomized double-blind controlled study, high-dose etanercept (100 mg/week) was as safe as the standard 50 mg/week dose, but without increased efficacy (ASAS 20 responder at week 12 with 100 vs 50 mg etanercept: 71 vs 76%) [42]. In addition, there is no evidence that adding a conventional treatment such as MTX is helpful in patients who failed to respond to TNF- α antagonists [43]. Adding MTX to infliximab did not influence pharmacokinetic parameters

(volume of distribution, systemic clearance and intercompartmental clearance) and did not influence the clinical response as evaluated by the BASDAI score [44]. Switching to another TNF- α antagonist is an option in nonresponders and has been proven to be effective: of 113 patients with AS receiving anti-TNF- α agents, 13% did not respond and thus were switched to a second drug, and 93% had a significant and sustained response [45]. Finally, the impact of the different TNF- α blocking agents on extra-articular manifestations is not equivalent. It has been demonstrated that etanercept is ineffective for IBD [46] and that this agent does not considerably reduce the incidence of acute anterior uveitis as compared with infliximab [47].

■ Predictive factors for response to TNF- α blockers in AS & SpA

Predictive factors have been identified from placebo-controlled trials and include young age, short disease duration, high BASDAI and elevated acute phase reactant levels (CRP), low BASFI and widespread inflammation of the spine as demonstrated by MRI [48,49]. Predictors of radiographic progression were assessed in a 2-year prospective study in a cohort of patients with AS or nonradiographic axial SpA. The presence of radiographic damage at baseline, elevated levels of acute phase reactants and cigarette smoking were identified as independent predictive factors for syndesmophyte progression. The authors proposed a prediction matrix model for this association with elevated ESR or CRP, with presence of syndesmophyte at baseline and cigarette smoking being the worst combination, resulting in a 55% risk of progression [50].

■ Long-term efficacy of TNF- α blockers in AS & SpA

Interestingly, a retrospective analysis of the efficacy of TNF- α antagonists in AS and psoriatic arthritis against RA demonstrated a higher efficacy of these agents in the treatment of SpA [51]. Reports of long-term efficacy of TNF- α -blocking agents are now available with open-label extensions of randomized controlled trials. In an 8-year extension study with infliximab in AS, half of the patients (48%) remained under treatment with clinical control of the disease, remission or low disease activity (BASDAI <3). In this analysis, adverse events remained the most frequent reason for withdrawal. Short-term response to infliximab (i.e., a lower BASDAI at week 12) was predictive of partial remission, low disease activity or remaining on treatment at year 8 [52].

■ Impact of TNF- α blockers on MRI inflammation & spinal ossifications

The available data clearly demonstrate a substantial reduction in spinal inflammation as shown by MRI in short-term and long-term anti-TNF- α administration [53]. However, a relevant question is whether TNF- α antagonists can control the progression of the disease in terms of development of spinal ossification. For ethical reasons, it is not authorized to maintain patients in a placebo group for a long period, which is necessary for evaluating the development of syndesmophytes. For these reasons, patients from randomized trials and under anti-TNF- α antagonists were compared with a historical cohort of patients (outcome of ankylosing spondylitis international study: OASIS) treated by conventional treatments. All the data were coherent and showed no difference in the progression of spinal ossifications between patients under anti-TNF- α agents and those from the OASIS cohort [54–56]. The mSASSS score was used to evaluate radiographic scores. There were methodological problems with these results due to the use of a historical cohort and the limited sensitivity to changes in the mSASSS. In addition, the mSASSS does not evaluate syndesmophytes at a thoracic level, a spinal segment where syndesmophytes usually appear, and only bone formation is evaluated and not bone/vertebral destructive changes. On the other hand, no data are available on the impact of TNF- α blockers (or NSAIDs) on the progression of sacroiliitis. However, recent data indicated that anti-TNF- α may partially control the vertebral destructive changes in patients with AS [57]. Interestingly, a recent study suggested that a TNF- α -blocking agent may have a protective effect on radiographic progression of hip arthritis in AS: 23 patients with hip involvement were evaluated before and after infliximab treatment. Hip structural damage was assessed using the Bath AS radiology hip index. This score remained stable over the 6-year follow-up period, suggesting a possible cartilage protective effect of infliximab. However, there was no control group in this study [58].

■ Safety of TNF- α -blocking agents in AS & SpA

The safety of TNF- α -blocking agents in AS is well documented. Placebo-controlled trials, open-label extension studies, long-term follow-up studies of AS patients under TNF- α blockers, biologics registries and meta-analyses have provided substantial data about their general safety. Infections and injection-related

reactions have been described and are the two major concerns in patients receiving TNF- α -blocking agents [36]. The risk of nonserious infections occurring during treatment with TNF- α blockers appears to be elevated during the placebo-controlled phases of the trials, while it decreases during the open-label phases, reaching a similar incidence in those registered in the placebo arm of randomized controlled studies. By contrast, the analysis of serious infections was higher for TNF- α blockers during randomized controlled trials, a difference, albeit small, that did not persist during the open-label phases of the trials (meta-analysis of serious infections for anti-TNF- α vs placebo treatment: risk difference 0.4%; 95% CI: -8 to 1.6%) [39]. Formation of antibodies against TNF- α blockers is another concern for the long-term safety and efficacy of these agents. Such antibodies came to light during randomized controlled trials, mainly with infliximab and adalimumab. They were not detected during or after treatment with etanercept. The presence of such antibodies was correlated with infusion- or injection-related reactions and with anti-TNF- α inefficacy. In a cohort of patients with SpA treated with infliximab and after a mean follow-up of 7 years, antibodies to infliximab were observed in 25% of patients and were associated with a poor clinical response, appearance of infusion reactions and discontinuation of treatment [59].

■ TNF- α blockers in patients with recent-onset disease

One relevant question is the usefulness of early intervention for patients with AS and SpA. The new classification criteria for axial and peripheral SpA [5,6] helps with early diagnosis. The question is whether a diagnosis at an early stage of the disease and thus rapid management could reduce the long-term consequences, especially structural damage and functional limitation. It has been determined that AS patients with short disease duration are more likely to respond to TNF- α -blocking agents [49]. In addition, anti-TNF- α monoclonal antibodies have been proven to be effective in patients with early axial disease, diagnosed based on MRI evidence of active inflammation of the spine or sacroiliac joints and in the absence of radiographic sacroiliac changes: adalimumab 40 mg every other week gave an ASAS20 responder rate of 54.2% compared with 12.5% in the placebo group [60]. In the ABILITY study, which enrolled patients with nonradiographic axial SpA, adalimumab was associated with a better ASAS40 response

compared with placebo (36 vs 15%). In parallel, there was a significant clinical improvement as assessed by ASDAS or BASDAI, sacroiliac joint inflammation on MRI and quality of life [61]. The results were similar with infliximab in patients with early disease, with 56% of patients in partial remission at week 16 of treatment [62]. Another study demonstrated the beneficial effects of SLZ on axial disease in patients with early AS and undifferentiated SpA [27]. All these data suggest that AS can be diagnosed and treated very early. An early diagnosis of AS or SpA can be of great benefit to the patient: it may have a favorable psychological impact; it may avoid the repetition of certain imaging procedures such as spine computed tomography required for low back pain assessment; it may improve quality of life sooner; it may help quickly identify a severe disease or a patient with poor prognostic factors, thus enabling appropriate treatment to be administered; and finally, an early intervention has the potential to reduce disability, to maintain the patient at work and to reduce medical and socioeconomic costs. However, whether or not an early intervention can reduce the progression of the disease in terms of structural damage has not been demonstrated. In RA, it is now established that early intervention with an aggressive treatment is useful for patients with the so-called 'window of opportunity' for adequate treatment. It has not been established whether such a window of opportunity exists in AS. A Canadian team has demonstrated that spinal bone formation is more likely to occur in advanced inflammatory lesions preceding syndesmophyte development or progression. According to this hypothesis, inflammation paves the way for bone formation, and thus controlling inflammation as early as possible may avoid structural progression, suggesting the existence of a window of opportunity in disease modification [63]. However, this theory is not validated by the discrepancy between resolution of MRI inflammation and radiographic progression under TNF- α -blocking agents.

Other therapeutic modalities in AS & SpA: nonpharmacological treatments

■ The nonpharmacological treatment options for AS & SpA

Education has an important role in AS, ensuring patients are informed about the diagnosis, prognosis and therapeutic options. Patient education has been proven to improve short-term function in one study [64]. Interdisciplinary meetings with different specialists and physicians

(rheumatologists, surgeons, rehabilitation specialists, physiotherapists, psychologists and staff involved in social assistance) are currently available in teaching hospitals for patient education programs to improve patient self-management [2,65,66].

Physical treatment is considered essential and should be regarded as first-line therapy in the management of AS, especially in patients with axial disease [2–4,7,67–70]. A Cochrane review concluded that home-based or supervised exercise programs are better than no intervention at all on pain, function, spinal mobility and overall patient assessment. Different approaches may be proposed but guided and supervised physical therapy is more effective than individual home exercise [71]. It is thus recommended that patients with predominant axial disease be managed by a physiotherapist, at least in the first few years of the disease, in order to learn specific exercises. This rehabilitation program will be efficacious on different outcomes including return to work and leads to economic advantages. Various types of exercise (in supervised groups, home and overall posture re-education) have moderate to good effects on BASDAI and BASFI, with a level of evidence between 3 and 1b [28]. According to the studies, effect size for outcome measures are not always significant, showing only a trend. Balneotherapy is moderately effective on BASDAI, BASFI and pain, with a 1b level of evidence but a nonsignificant effect size [28].

■ Place of nonpharmacological therapeutic options in AS & SpA

Physiotherapy must be regarded as first-line treatment in AS [70]. The nonpharmacological therapeutic options complement pharmacological treatments in AS and must be systematically proposed to patients according to the clinical presentation and to the functional limitation induced by the disease [101]. Medical social actions, such as reimbursements of health expenses and assistance adapting to work, are often useful for the patient [101].

Biologics other than anti-TNF- α in AS & SpA

■ Biologics other than TNF- α blockers in AS & SpA

It is understood that approximately 20–25% of patients do not respond adequately to TNF- α antagonists and may be considered as refractory to these agents [36]. Alternative therapeutic options in AS are scarce. Besides TNF- α -blocking agents, we have limited data on the effectiveness of other biologic agents in AS and only small and uncontrolled studies have been conducted in AS patients (TABLE 2). There are no data on other forms of SpA, but some of these compounds have been approved for the treatment of RA or psoriatic arthritis.

Results with anakinra, the IL-1 receptor antagonist, are not encouraging. In an open study performed in Germany, 20 patients

Table 2. Biologics other than TNF blockers that have been evaluated for use in ankylosing spondylitis. Results of clinical trials.

Biologic	Study (year)	Study design	Patients (n)	Primary outcome	Results (responders/nonresponders or % of responders)	Ref.
Anakinra	Haibel <i>et al.</i> (2005) Tan <i>et al.</i> (2004)	Open-label studies	20 9	ASAS20 responders at week 24 or 12	5/20 6/9	[72] [73]
Rituximab	Song <i>et al.</i> (2010)	Open-label study	20	ASAS40 responder at week 24	TNF naive: 50 TNF failure: 30	[74]
Abatacept	Song <i>et al.</i> (2011)	Open-label study	30	ASAS40 responder at week 24	3–4	[76]
Tocilizumab	Sieper <i>et al.</i> (2012)	Randomized placebo-controlled study	102	ASAS20 at week 12	Tocilizumab: 37 Placebo: 28	[77]
Sarilumab	Sieper <i>et al.</i> (2012)	Randomized placebo-controlled study	301	ASAS20 at week 12	Placebo 28 Sarilumab: 22–33	[78]
Secukinumab	Baeten <i>et al.</i> (2010)	Randomized placebo-controlled study proof of concept	30	ASAS20 at week 6	Secukinumab: 14/23 Placebo: 1/6	[79]
Apremilast	Pathan <i>et al.</i> (2011)	Unpowered pilot study Phase II	36	Change in BASDAI, BASFI and BASMI at week 12	Positive changes in the apremilast group	[81]

ASAS: Assessment in SpondyloArthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index.

received 100 mg of anakinra for 24 weeks, with no improvement for most of the patients [72]. A second study enrolled nine patients and six achieved an ASAS20 response at 3 months. In this study, a 61% reduction in spinal and/or sacroiliac joint MRI inflammation was observed [73]. The conclusion of these open studies is that anakinra is mildly efficacious, but randomized controlled studies are still lacking.

Rituximab has been similarly evaluated in open label studies. In a German study, ten anti-TNF- α naive and ten anti-TNF- α refractory patients received 1000 mg of rituximab intravenously at baseline and at week 2. Only the TNF- α -naive patients were responders according to the ASAS20 response [74]. The 1-year follow-up of these responding patients showed that half of them flared and required a second course of rituximab. These patients responded well to this second round of rituximab treatment. In the initial responders who did not flare, clinical response was stable for 1 year [75].

The costimulatory pathway inhibitor abatacept has been tested in an open-label study. However, it was found to be ineffective: 15 anti-TNF- α -naive patients and 15 patients with an inadequate response to anti-TNF- α therapy received abatacept 10 mg/kg. Only 13% in the naive group were ASAS40 responders, while no patients in the TNF- α failure group reached the primary end point [76].

It was believed that IL-6 could be an attractive therapeutic target in AS. The rationale for targeting this cytokine is that patients with AS have elevated circulating IL-6 levels that correlate with disease activity. Two unpublished randomized placebo-controlled trials have evaluated the efficacy in AS of IL-6-blocking agents: tocilizumab and sarilumab, respectively. However, these trials were interrupted at week 12 because the primary end point was not achieved. For both trials, there was no difference in ASAS20 response between the biologic and the placebo [77,78].

Secukinumab is an anti-IL-17A monoclonal antibody. Circulating IL-17 has been found to be elevated in patients with AS. Secukinumab has been tried in a placebo-controlled trial including 24 patients with AS. These patients were NSAID-refractory. In total, 60% of patients in the treatment group were ASAS20 responders compared with 17% in the placebo group [79]. However, the statistical analysis involved a Bayesian (not an intent to treat) analysis. In addition, secukimab was associated with a reduction in spinal inflammation on MRI after

6 weeks of treatment and this was maintained up to week 28 [80].

Apremilast is a phosphodiesterase-4 inhibitor that can reduce TNF- α production. This orally administered drug has been evaluated in AS in a double-blind placebo-controlled study in patients with advanced disease. A trend was observed for a greater improvement in all clinical outcomes in the apremilast group compared with the placebo arm [81].

Besides these biologic agents, the amino-bisphosphonate pamidronate has a controversial place in the treatment of AS: it has been evaluated in a controlled study (pamidronate 60 mg vs pamidronate 10 mg), giving favorable results for all clinical assessments. However, these results have not been confirmed by any other study or other groups (for a review, see [82]).

■ When & for which patients?

There is currently no proof of the efficacy of these agents in AS, and they are thus not recommended in patients with AS, even in the event of TNF- α antagonist failure. According to these results, the strength of recommendation for the use of these alternative biologics in AS was rated as C by the ASAS/EULAR groups [39].

Discussion

The therapeutic management of AS and related SpA is currently well codified, with specific recommendations established by scientific societies or official health agencies. Overall, there is considerable evidence in favor of NSAIDs and anti-TNF- α agents for AS [83]. However, specific questions about the therapeutic management of AS and SpA are unanswered.

In patients with persistent and active disease, whether or not continuous and long-term NSAID treatment can be administered should be discussed. The benefit/risk ratio must be estimated in this situation according to patient age, the presence of comorbidities and comedication intake. In particular, the cardiovascular safety of long-term NSAID administration should be kept in mind. In the context of persistent disease requiring daily treatment, initiating a TNF- α -blocking agent rather than giving continuous NSAID treatment could be an option. However, there are no data available comparing the safety of long-term anti-TNF- α administration with continuous NSAID treatment. Recent studies have demonstrated that continuous NSAIDs may control radiographic progression in AS. This property of NSAID must be taken into account, but the current position of the different scientific

societies and health authorities is to reserve NSAID treatment for a flare of the disease and to stop it when the symptoms are resolved [7–9,101].

The influence of the therapeutic options in AS on structural damage is still debated, particularly for TNF- α antagonists [2–4,36,84]. The link between spinal inflammation and development of syndesmophytes is increasingly studied and it has been hypothesized that some specific markers involved in bone formation such as sclerostin and DKK-1 may play a role [85,86]. Of note, these bone remodeling molecules are partially independent from the TNF- α pathway and this may explain why the control of spinal inflammation in AS did not parallel syndesmophyte progression.

The therapeutic recommendations for AS and SpA by the ASAS/EULAR groups are regularly revised and have thus evolved: one main modification in the updated version of the ASAS recommendations is the need to test two NSAIDs over a 4-week period before initiating a TNF- α -blocking agent [87]. The maximum NSAID effect is achieved after 2 weeks, but this time period for testing NSAID response in AS may be too short. Clinicians thus have some flexibility on how long to use NSAIDs in their patients, and a time period ranging from 4 to 8 weeks seems more

appropriate. In addition, it must be remembered that in most countries, TNF- α -blocking agents are only approved and licensed only for patients with established disease and thus with radiographic sacroiliitis. However, the European Commission recently recommended adalimumab to be used in patients with nonradiographic SpA who failed to conventional treatments.

New therapeutic options are urgently needed. In fact, there is currently no alternative for patients who are refractory to TNF- α -blocking agents or to NSAIDs [39,88]. Since most of the data on the clinical efficacy of biologics other than anti-TNF- α in AS comes from open-label studies, adequate randomized placebo-controlled trials are required.

Conclusion

The therapeutic management of AS and SpA has progressed considerably over the past 10 years with the development of TNF- α blockers. NSAIDs remain the reference drug class that must be proposed as a first-line treatment. TNF- α antagonists are highly effective on all the clinical symptoms of the disease, with a favorable safety profile. For the domains of pain, physical function and patient's overall assessment, the effect size of

Executive summary

Current therapeutics for ankylosing spondylitis & spondyloarthritis

- Ankylosing spondylitis (AS) belongs to a clinically related group of disorders named spondyloarthritis (SpA) mainly affecting the axial skeleton and presenting with specific extra-articular manifestations. The therapeutic management of AS and other types of SpA has improved considerably over the past 10 years. The different available treatments for AS, including traditional treatments (NSAIDs, sulfasalazine and methotrexate, and local corticosteroids) and biological therapies (TNF- α antagonists), as well as nonpharmacological procedures (education and physical therapy) are discussed in this article in light of the level of evidence for their use in AS and SpA and according to specific published international recommendations.

NSAIDs & TNF- α in the treatment of AS & SpA

- Together with physiotherapy, NSAIDs remain the first-line treatment in AS, especially in patients with axial disease. There is an increasing amount of evidence showing the short-term and long-term efficacy of TNF- α antagonists in AS, with control of pain, extra-articular manifestations and systemic and spinal MRI inflammation.

Structural damage & NSAIDs & TNF- α -blocking agents in AS

- There is no proof that anti TNF- α agents can control radiographic progression in the spine. Alternatively, continuous administration of NSAIDs seems able to delay spinal bone formation.

Patients with early disease & alternative to biologics other than anti-TNF- α

- Although they are not recognized diagnosis criteria, the new classification criteria for SpA helps with an early diagnosis. TNF- α blockers are currently being tested in these patients with early disease, with favorable clinical results. Since approximately 20–25% of AS patients are considered as non-major responders to TNF- α blockers, there is an unmet need for alternative therapies.

NSAIDs are the cornerstone medication in AS & SpA

- There are now three studies suggesting that continuous NSAID treatment may delay spinal radiographic progression in AS.
- Traditional disease-modifying anti-rheumatic drugs including sulfasalazine and methotrexate are not very effective in AS, especially in axial disease. Sulfasalazine may be proposed in patients with peripheral arthritis.
- Anti-TNF- α agents are highly effective for the different clinical manifestations of AS and SpA. There is accumulating evidence suggesting a role for TNF- α -blocking agents in patients with early disease.
- There is no proof that anti-TNF- α agents can control the progression of spinal ossifications.
- Alternative therapies are scarce in AS and SpA.

both TNF- α blockers and NSAIDs is large or medium, while for the domain of mobility, it is small [83]. The number needed to treat for one AS patient to benefit from anti-TNF- α clinically is between one and two [3,83].

Future perspective

The impact of the anti-TNF- α agents on the progression of spinal ossifications is not currently demonstrated and remains debated, while NSAIDs agents seem capable of slowing down this progression [11,20–22]. More studies concerning this are needed to better understand

the mechanisms explaining spinal bone formation in AS. Blocking TNF- α is also effective in the treatment of early disease stages, but whether an early intervention in these patients will benefit them or not needs to be demonstrated. New (biological) treatments are needed for AS to provide alternative options for patients who fail to respond to NSAID/TNF- α blockers.

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- 101 Diagnostic, prise en charge thérapeutique et suivi des spondylarthrites. Haute Autorité de Santé. www.has.fr
- **Official recommendations for the management of AS published by the French Health Authority.**



Therapeutics for the treatment of spondyloarthritis: what, when and whom

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 68-year-old male with ankylosing spondylitis (AS). Based on the review by Drs. Toussiro and Michel, which of the following statements about use of nonsteroidal anti-inflammatory drugs (NSAIDs) in his management is **most likely** correct?

- ☐ A Expert groups and scientific committees recommend NSAIDs as the first-line pharmacological treatment to improve pain and stiffness in AS and spondyloarthritis (SpA)
- ☐ B It takes several weeks of continuous treatment for NSAIDs to become effective, and efficacy diminishes over time
- ☐ C There is no evidence that continuous NSAID treatment delays spinal radiographic progression in AS
- ☐ D Studies have shown that phenylbutazone is superior to other NSAIDs for management of AS

2. Based on the review by Drs. Toussiro and Michel, which of the following statements about the role of pharmacological treatments other than NSAIDs, physical therapy, and other non-pharmacological procedures in the management of the patient described in question 1 is **most likely** correct?

- ☐ A Physical therapy is not recommended
- ☐ B Traditional disease modifying anti-rheumatic drugs (DMARDs) are highly effective in AS patients with axial disease
- ☐ C High-dose systemic corticosteroids are effective in AS
- ☐ D Local corticosteroid injection may be indicated for patients with resistant enthesitis or refractory sacroiliac pain

- 3 Based on the review by Drs. Toussiroot and Michel, which of the following statements about the role of tumor necrosis factor (TNF)-alpha blocking agents and other biological agents in the management of AS and SpA would **most likely** be correct?
- ☐ A Anti-TNF-alpha agents have been proven to control radiographic progression of spinal ossifications
 - ☐ B Anti-TNF-alpha agents help to control pain, extra-articular manifestations, and systemic and spinal MRI inflammation in patients with AS
 - ☐ C Anti-TNF-alpha agents are effective in AS in the short term but not in the long term
 - ☐ D There is a wide range of alternative therapies available in AS and SpA