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

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Abstract

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

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

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> **Rheumatology key messages**
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> - The first-line therapy for axial spondyloarthritis is physiotherapy and NSAIDs.
> - Not all patients with axial spondyloarthritis respond well to anti-TNF therapy.
> - Anti-IL-17 therapy is an approved treatment for patients with ankylosing spondylitis.

REVIEW

Introduction

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

First-line therapy for axSpA: physiotherapy and NSAIDs

The optimal management of patients with SpA requires a combination of pharmacological and non-pharmacological

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

Joint recommendations from the Assessment of SpondyloArthritis international Society (ASAS) and the EULAR state that regular physical exercise and patient education should form the cornerstone of optimal treatment [5]. Furthermore, studies have shown that home-based exercise interventions can effectively improve health-related quality of life [6]. However, to improve adherence, supervised programmes (whether individual or in

a group) may be more effective than home-based approaches [7]. In addition, contact with patient support groups should be encouraged, as this has the potential to improve motivation and compliance within the context of a long-term condition. A recent Cochrane review found that any exercise, whether supervised or home-based, is better than no exercise for improving movement and physical function [8]. The National Ankylosing Spondylitis Society has also highlighted the importance of access to hydrotherapy [3], which has been shown to improve disease activity and functional parameters in AS [9].

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

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

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

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

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

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

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

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

Conventional synthetic DMARDs in axSpA

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

additional efficacy is conferred when MTX is combined with TNF inhibitor (TNFi) therapy [36].

TNFi therapy in axSpA

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

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

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

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

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

switching TNFi therapy can work, but diminishing returns are typical.

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

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

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

The effect of TNFi therapy on radiographic progression in axSpA is currently unclear. In one study following 334 patients treated with standard therapies for AS, 201 of whom received TNFi therapy, there was a 50% reduction in the odds of radiographic progression with the TNFi compared with standard therapy [51]. Another study conducted in patients with AS showed that TNFis are associated with a reduction in spinal radiographic damage [52]. However, numerous other studies have shown no effect of TNFi therapy on structural progression in AS [53–55]. One possible limitation of these studies is that TNFi therapy may be necessary for 4 years before any benefit on radiographic progression becomes apparent [56].

TABLE 1 Seminal randomized controlled clinical trials evaluating the efficacy of TNFis in patients with AS

Generic name	Trial	Main inclusion criteria	Number of patients in active arm/ comparator arm	Primary endpoint	Primary endpoint vs PBO	References
Adalimumab[a]	ATLAS	Active AS, inadequate response to glucocorticoids, NSAIDs, analgesics, MTX or SSZ	208/107	ASAS 20 at week 12 vs PBO	58.2 vs 20.6%	[5]
Certolizumab pegol[b]	RAPID-axSpA	Active AS and nr-axSpA, elevated CRP levels and/or sacroiliitis on MRI, inadequate response to one or more NSAIDs	111 (200 mg Q2W) 107 (400 mg Q4W)/107	ASAS 20 at week 12 vs PBO	57.7% (200 mg Q2W) 63.6% (400 mg Q4W) vs 38.3%	[1]
Etanercept[a]	Enbrel AS study group trial	Active AS	138/139	ASAS 20 at week 12 vs PBO	57 vs 22%	[37]
Golimumab[a]	GO-RAISE	Active AS with inadequate response to NSAIDs or DMARDs	138 (50 mg Q4W) 140 (100 mg Q4W)/78	ASAS 40 at week 14 vs PBO	59.4% (50 mg Q2W) 60.0% (100 mg Q4W) vs 21.8%	[38]
Infliximab	ASSERT	Active AS, normal chest radiograph, negative for latent tuberculosis	201/78	ASAS 20 at week 24 vs PBO	61.2 vs 19.2%	[39]
In patients with early/nr-axSpA						
Infliximab	—	Recent-onset inflammatory back pain, HLA-B27-positive, MRI evidence of sacroiliitis	20/20	Change in total MRI score at week 16 vs PBO	−2.0 vs 0.0	[40]
Etanercept	ESTHER	Diagnosis of axSpA with symptom duration of <5 years, good or very good response to NSAIDs	40/36	Change in active inflammatory lesions in the SI joints and spine detected by MRI at week 48 vs SSZ	−5.7 vs −1.9	[11]
Infliximab	INFAST (part 1)	Moderate to severe active axSpA with disease duration ≤3 years, not refractory to NSAIDs	105/51	ASAS partial remission at week 28 vs PBO	61.9 vs 35.5%	[12]
Adalimumab	—	Active axSpA without radiographically defined sacroiliitis, refractory to NSAIDs	22/24	ASAS 40 at week 12 vs PBO	54.5 vs 12.5%	[43]

Data taken from references 1, 5, 37–43. These data do not come from a direct head-to-head comparison. These data are from the pivotal placebo-controlled studies for each biologic listed; the study design, including inclusion/exclusion criteria and baseline characteristics may be different. [a]All patients enrolled into these trials had not received any anti-TNF therapy before randomization. [b]In addition to patients with AS (n = 178), patients with nr-axSpA (n = 147) were included in this trial; combined results were presented in this trial. ASAS: Assessment of SpondyloArthritis International Society; axSpA: axial spondyloarthritis; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks.

The impact of TNFi therapies on work participation in patients with AS has also been analysed in a recent systematic review [57]. Short-term productivity loss at work (presenteeism), absence from paid work and long-term employment status were assessed. Thirty-nine comparisons were reviewed, in nine studies, with most comparisons suggesting positive work outcomes with treatment, although these effects were not tested for statistical significance. Further studies are required to evaluate the effect of TNFi therapy on work-related outcomes in patients with long-standing AS.

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

Anti-IL-17 therapy in axSpA

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

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

conclusions can be made as to whether anti-IL-17 therapy is effective in inhibiting radiographic progression.

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

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

References

1 Landewé R, Braun J, Deodhar A *et al.* Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. Ann Rheum Dis 2014;73:39–47.

2 Kiltz U, Heldmann F, Baraliakos X, Braun J. Treatment of ankylosing spondylitis in patients refractory to TNF-inhibition: are there alternatives? Curr Opin Rheumatol 2012;24:252–60.

3 National Ankylosing Spondylitis Society. Looking Ahead: Best Practice for the Care of People with Ankylosing Spondylitis. http://nass.co.uk/campaigning/looking-ahead/ (November 2017, date last accessed).

4 Hamilton L, Barkham N, Bhalla A *et al.* BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology 2016;56:313–6.

5 van der Heijde D, Kivitz A, Schiff MH *et al*. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:2136–46.

6 Liang H, Zhang H, Ji H, Wang C. Effects of home-based exercise intervention on health-related quality of life for patients with ankylosing spondylitis: a meta-analysis. Clin Rheumatol 2015;34:1737–44.

7 Sollini N, Nava T, Parlatoni A, Moretti V, Scendoni P. Is group-based exercise better than home-based exercise in patients with ankylosing spondylitis stabilized with tumor necrosis factor-alpha inhibitor therapy? A randomized controlled study. Ann Rheum Dis 2015;74:417.

8 Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database Syst Rev 2008;1:CD002822.

9 Altan L, Bingöl U, Aslan M, Yurtkuran M. The effect of balneotherapy on patients with ankylosing spondylitis. Scand J Rheumatol 2006;35:283–9.

10 Spencer S, Martindale J, MacPhie E, Montgomery P. Self management programme for ankylosing spondylitis. Cochrane Database Syst Rev 2015;12:CD006977.

11 Song IH, Poddubnyy DA, Rudwaleit M, Sieper J. Benefits and risks of ankylosing spondylitis treatment with non-steroidal antiinflammatory drugs. Arthritis Rheum 2008;58:929–38.

12 Sieper J, Lenaerts J, Wollenhaupt J *et al*. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, part 1. Ann Rheum Dis 2014;73:101–7.

13 Braun J, Berg R, van den Baraliakos X *et al*. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70:896–904.

14 Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? Ther Adv Musculoskelet Dis 2013;5:45–54.

15 Sieper J, Klopsch T, Richter M *et al*. Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study. Ann Rheum Dis 2008;67:323–9.

16 Barkhuizen A, Steinfeld S, Robbins J *et al*. Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. J Rheumatol 2006;33:1805–12.

17 Jarrett SJ, Sivera F, Cawkwell LS *et al*. MRI and clinical findings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. Ann Rheum Dis 2009;68:1466.

18 Baraliakos X, Kiltz U, Peters S *et al*. Efficiency of treatment with non-steroidal anti-inflammatory drugs according to current recommendations in patients with radiographic and non-radiographic axial spondyloarthritis. Rheumatology 2017;56:95–102.

19 Boersma JW. Retardation of ossification of the lumbar vertebral column in ankylosing spondylitis by means of phenylbutazone. Scand J Rheumatol 1976;5:60–4.

20 Wanders A, van der Heijde D, Landewé R *et al*. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum 2005;52:1756–65.

21 Sieper J, Listing J, Poddubnyy D *et al*. Effect of continuous versus on-demand treatment of ankylosing spondylitis with diclofenac over 2 years on radiographic progression of the spine: results from a randomised multicentre trial (ENRADAS). Ann Rheum Dis 2016;75:1438–43.

22 Kroon FP, van der Burg LR, Ramiro S *et al*. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). Cochrane Database Syst Rev 2015;17:CD010952.

23 Bjorkman D. Nonsteroidal anti-inflammatory drug-associated toxicity of the liver, lower gastrointestinal tract, and esophagus. Am J Med 1998;105(5 Suppl 1):17S–21S.

24 Silverstein FE, Faich G, Goldstein JL *et al*. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247–55.

25 Whelton A. Renal aspects of treatment with conventional nonsteroidal anti-inflammatory drugs versus cyclooxygenase-2-specific inhibitors. Am J Med 2001;110(Suppl 3A):33S–42S.

26 Goldstein JL, Correa P, Zhao WW *et al*. Reduced incidence of gastroduodenal ulcers with celecoxib, a novel cyclooxygenase-2 inhibitor, compared to naproxen in patients with arthritis. Am J Gastroenterol 2001;96:1019–27.

27 Solomon SD, McMurray JJV, Pfeffer MA *et al*. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.

28 FDA. Proposed NSAID Package Insert Labeling Template. 1996. https://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_03_D-FDA-TAB-B.pdf(March2018, date last accessed).

29 Regel A, Sepriano A, Baraliakos X *et al*. Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. RMD Open 2017;3:e000397.

30 Nissen SE, Yeomans ND, Solomon DH *et al*. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016;375:2519–29.

31 FDA. Proposed NSAID Package Insert Labeling Template. http://www.fda.gov/downloads/drugs/drugsafety/post-marketdrugsafetyinformationforpatientsandproviders/ucm106230.pdf (November 2018, date last accessed).

32 Fagerli KM, van der Heijde D, Heiberg MS *et al*. Is there a role for sulphasalazine in axial spondyloarthritis in the era of TNF inhibition? Data from the NOR-DMARD longitudinal observational study. Rheumatology 2014;53:1087–94.

33 Braun J, Zochling J, Baraliakos X *et al*. Efficacy of sulfasalazine in patients with inflammatory back pain due to

undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. Ann Rheum Dis 2006;65:1147–53.

34 Chen J, Lin S, Liu C. Sulfasalazine for ankylosing spondylitis. Cochrane Database Syst Rev 2014;27: CD004800.

35 Haibel H, Brandt HC, Song IH et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. Ann Rheum Dis 2007;66:419–21.

36 Marzo-Ortega H, McGonagle D, Jarrett S et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. Ann Rheum Dis 2005;64:1568–75.

37 Davis JC, van der Heijde D, Braun J et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003;48:3230–6.

38 Inman RD, Davis JC, van der Heijde D et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008;58:3402–12.

39 van der Heijde D, Dijkmans B, Geusens P et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum 2005;52:582–91.

40 Barkham N, Keen HI, Coates LC et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. Arthritis Rheum 2009;60:946–54.

41 Song I-H, Hermann K, Haibel H et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 2011;70:590–6.

42 Sieper J, Lenaerts J, Wollenhaupt J et al. Double-blind, placebo-controlled, 28-week trial of efficacy and safety of infliximab plus naproxen vs naproxen alone: results from the infliximab as first line therapy in patients with early, active axial spondyloarthritis trial, part I. Arthritis Rheum 2012;64:S1–1216.

43 Haibel H, Rudwaleit M, Listing J et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. Arthritis Rheum 2008;58:1981–91.

44 Brandt J, Khariouzov A, Listing J et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 2003;48:1667–75.

45 NICE guidance for AS. Available at: https://www.nice.org.uk/guidance/ng65/chapter/recommendations.

46 Glintborg B, Østergaard M, Krogh NS et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor α inhibitor therapy: results from the Danish nationwide DANBIO registry. Ann Rheum Dis 2013;72:1149–55.

47 Baraliakos X, Listing J, Brandt J et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005;7:R439.

48 Breban M, Vignon E, Claudepierre P et al. Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. Rheumatology 2002;41:1280–5.

49 Sieper J, Lenaerts J, Wollenhaupt J et al. Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST part 2. Ann Rheum Dis 2014;73:108–13.

50 Song I-H, Althoff CE, Haibel H et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis 2012;71:1212–5.

51 Haroon N, Inman RD, Learch TJ et al. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum 2013;65:2645–54.

52 Molnar C, Scherer A, Baraliakos X et al. TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: results from the Swiss Clinical Quality Management cohort. Ann Rheum Dis 2018;77:63–9.

53 Braun J, Baraliakos X, Hermann K-GA et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. Ann Rheum Dis 2014;73:1107–13.

54 van der Heijde D, Salonen D, Weissman BN et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther 2009;11:R127.

55 van der Heijde D, Landewé R, Einstein S et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324–31.

56 Baraliakos X, Heldmann F, Callhoff J et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 2014;73:1819–25.

57 van der Burg LRA, ter Wee MM, Boonen A. Effect of biological therapy on work participation in patients with ankylosing spondylitis: a systematic review. Ann Rheum Dis 2012;71:1924–33.

58 Ding T, Ledingham J, Luqmani R et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology 2010;49:2217–9.

59 Ivanov S, Lindén A. Interleukin-17 as a drug target in human disease. Trends Pharmacol Sci 2009;30: 95–103.

60 Hoshino H, Laan M, Sjöstrand M et al. Increased elastase and myeloperoxidase activity associated with neutrophil recruitment by IL-17 in airways in vivo. J Allergy Clin Immunol 2000;105:143–9.

61 Prause O, Bozinovski S, Anderson GP, Lindén A. Increased matrix metalloproteinase-9 concentration and activity after stimulation with interleukin-17 in mouse airways. Thorax 2004;59:313–7.

62 Ivanov S, Bozinovski S, Bossios A et al. Functional relevance of the IL-23-IL-17 axis in lungs in vivo. Am J Respir Cell Mol Biol 2007;36:442–51.

63 Shen H, Goodall JC, Hill Gaston JS. Frequency and phenotype of peripheral blood Th17 cells in ankylosing spondylitis and rheumatoid arthritis. Arthritis Rheum 2009;60:1647–56.

64 Appel H, Maier R, Wu P *et al*. Analysis of IL-17^{+} cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. Arthritis Res Ther 2011;13:R95.

65 Cosentyx 150 mg solution for injection in pre-filled syringe and pre-filled pen—summary of product characteristics (SPC)—(eMC). https://www.medicines.org.uk/emc/medi-cine/29848 (23 July 2018, date last accessed).

66 Baeten D, Baraliakos X, Braun J *et al*. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of anky-losing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet 2013;382:1705–13.

67 Baraliakos X, Braun J, Laurent DD *et al*. Interleukin-17A blockade with secukinumab reduces spinal inflammation in patients with ankylosing spondylitis as early as week 6, as detected by magnetic resonance imaging. Arthritis Rheum 2011;63:S972.

68 Baeten D, Sieper J, Braun J *et al*. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015;373:2534–48.

69 Braun J, Baraliakos X, Deodhar A *et al*. Effect of secuki-numab on clinical and radiographic outcomes in ankylos-ing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. Ann Rheum Dis 2017;76:1070–7.

70 Sieper J, Deodhar A, Marzo-Ortega H *et al*. Secukinumab efficacy in anti-TNF-naive and anti-TNF-experienced subjects with active ankylosing spondylitis: results from the MEASURE 2 study. Ann Rheum Dis 2017;76:571–92.

71 Baraliakos X, Kivitz AJ, Deodhar AA *et al*. Long-term ef-fects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial. Clin Exp Rheumatol 2018;36:50–5.