Guidelines

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BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics

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Key words: ankylosing spondylitis, axial spondyloarthritis, anti-TNF, biologic, guideline, treatment

Scope and purpose

Background

Axial SpA (axSpA) is a chronic inflammatory condition predominantly involving the spine and sacroiliac joints (SIJ), with or without extra-spinal manifestations including peripheral arthritis, enthesitis, iritis, psoriasis and IBD. Individuals with axSpA experience significant pain, stiffness and lack of function, which translates into important health care costs and increased mortality.

AxSpA can be classified into two subgroups: radiographic axSpA, commonly referred to as AS, and non-radiographic axSpA (nr-axSpA). The primary difference between these two subgroups is the presence or absence of defined structural changes in the SIJ as detected on plain radiography. A diagnosis of AS can be made according to the modified New York criteria when radiographs show at least grade 2 sacroiliitis bilaterally or grade 3 unilaterally, in the presence of appropriate clinical symptoms [1]. In contrast, SIJ radiographs may be completely normal in nr-axSpA. The radiographic changes of AS may take 8–10 years to manifest, with a progression rate from nr-axSpA to AS of ~12% every 2 years [2], although some patients with nr-axSpA never develop AS. Disease progression is predicted most strongly

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NICE has accredited the process used by the BSR to produce its treatment of axial spondyloarthritis with biologics guidance. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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GUIDELINES

by the presence of the HLA-B27 haplotype and severe sacroiliitis on MRI at clinical presentation [3].

The aims of treatment in axSpA are to reduce inflammation, relieve pain and stiffness, preserve spinal mobility and prevent the development of syndesmophytes. Although there is limited evidence that NSAIDs may slow the development of radiographic change [4], standard treatment is essentially symptomatic. In contrast to peripheral arthritis, DMARDs have no effect on symptoms or progression of axial disease [5, 6].

Need for updated guidelines

Several major developments have occurred since the publication of the previous British Society for Rheumatology (BSR) guidelines [7], necessitating a revision. First, the 2005 guidelines applied only to the subset of patients with established AS. However, the concept of axSpA has fundamentally changed in the past decade, primarily led by improvements in imaging techniques. A growing amount of data shows that patients with nr-axSpA suffer a similar disease burden [8] and may derive as much benefit from treatment as patients with established AS. To ensure best care, treatment guidelines should apply to the whole spectrum of axSpA. Additionally, according to current National Institute for Health and Care Excellence (NICE) guidance [9], AS patients may only switch to a second anti-TNF drug within the first 12 weeks of treatment, and then only if they suffer an adverse event. Recent published evidence now supports the sequential use of two or more anti-TNF drugs in patients who have failed to respond due to inefficacy or toxicity [10, 11], and continuing to deny patients effective treatment is untenable. Finally, the therapeutic arsenal has expanded over the past decade to include not just anti-TNF drugs, but other biologic agents and biosimilar drugs, and these have been included in the most recent literature search.

Objectives of the guidelines

These guidelines provide evidence-based guidance for UK clinicians prescribing biologics for adult patients with axSpA. This includes the criteria for starting treatment, the choice of drug and assessing response to treatment.

Peripheral SpA and juvenile SpA are outside the scope of these guidelines, and readers are referred to the BSR 2012 guidelines for the management of PsA [12]. While a systematic approach was adopted to assess the efficacy of biologic drugs in axSpA, this did not include a health economic evaluation.

Most safety concerns with anti-TNF therapies are common to their use in all inflammatory conditions, and to avoid overlap between BSR guidelines it has been decided that the generic safety aspects will be addressed by a separate BSR guideline on the safety of biologic therapies in inflammatory arthropathies [13] (currently under revision). These guidelines therefore consider only those safety aspects of specific relevance to axSpA.

Target audience

These guidelines are intended primarily for rheumatologists and other clinicians prescribing biologic drugs for the treatment of people with axSpA. However, they will also be of interest to specialist nurses, allied health professionals and general practitioners (GPs) involved in monitoring treatment and assessing response.

Stakeholder involvement

These guidelines have been written by a working party established by the BSR whose membership includes rheumatologists, allied health professionals, a GP, a patient representative and a representative from the National Ankylosing Spondylitis Society. Full details including conflicts of interest are listed at the end of this paper. The guidelines were presented for comment at the BSR Annual Meeting in 2015.

Rigour of Development

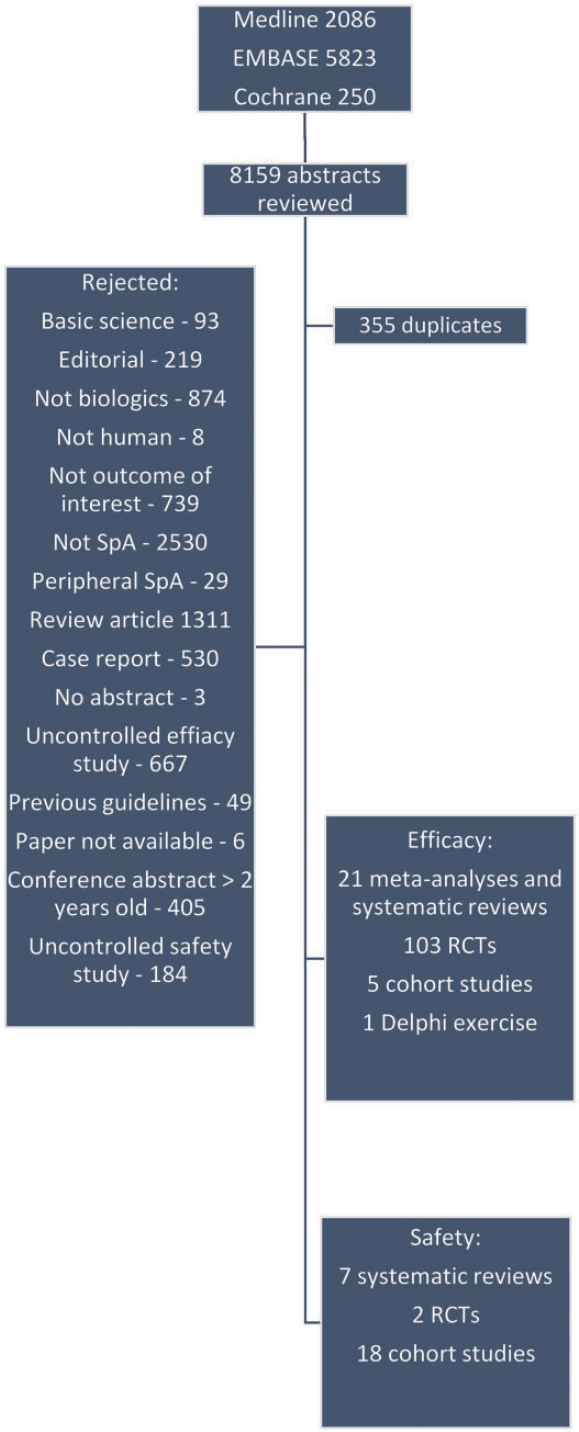
Scope of the literature search and strategy employed

The evidence for these guidelines is based on a systematic literature search of Medline, Embase and the Cochrane library up to 30 June 2014. The working group defined the terms of the search using a Patient Intervention Comparison Outcome format, where patients were individuals with AS or nr-axSpA, the intervention was biologics, the comparator was placebo and the outcomes were measures of disease activity, function, spinal mobility and radiological severity. Structured key questions were developed by the group as a whole (individual questions are listed in Appendix 1) with search terms as follows: (SPONDYLITIS, ANKYLOSING/OR AS OR spondyloarthr* OR spondylarthr* OR SpA OR sacroiliitis) AND (infliximab OR remicade OR etanercept OR enbrel OR adalimumab OR humira OR certolizumab OR cimzia OR abatacept OR orencia OR golimumab OR simponi OR tocilizumab OR roactemra OR ustekinumab OR stelara OR efalizumab OR raptiva OR anakinra OR kineret OR alefacept OR amevive OR rituximab OR mabthera OR anti-TNF or 'TNF inhibitor' OR biologic).

The search was limited to articles in English. Outcomes of interest were efficacy in AS (including total ankylosis) and nr-axSpA, comparing biologics, switching and withdrawing treatment, intermittent and changed dosing, predictors of response, outcome measures including radiographic outcomes, effect on extra-articular features, work productivity and absenteeism, utilization of health care (all categorized as efficacy in Fig. 1), as well as side effects, vaccine safety, reproductive safety and safety in patients with viral hepatitis or HIV (grouped as safety in Fig. 1). The search terms and outcomes of interest were agreed upon by the working group in advance of the literature search.

For efficacy outcomes, only high-quality meta-analyses, systematic reviews or randomized controlled trials (RCTs) were considered, unless no other data were available for a particular outcome, in which case observational studies with control arms were reviewed. For safety outcomes, controlled observational studies were accepted. Conference abstracts less than 2 years old were accepted unless the same data had been subsequently published.

Fig. 1 Results of systematic literature review



Titles and abstracts were screened and relevant full papers were each graded by two members according to the system used by the Scottish Intercollegiate Guidelines Network (SIGN) [14] (Table 1). A summary of the results of the literature search is shown in Fig. 1.

Based on the literature review, the working party developed recommendations for treatment. All members then anonymously stated their level of agreement with each statement on a 0–10 scale, where 10 is total agreement. The resulting consensus scores are given for each recommendation below.

Statement of extent of NICE, Royal College of Physicians and SIGN guidelines

Since the last BSR guidelines, NICE has published guidelines for biologics in AS [TA 143 (2008), currently being updated] and the Assessment of SpondyloArthritis international Society (ASAS) and EULAR produced updated guidelines in 2010 that included the treatment of non-radiographic disease [16]. There have been no SIGN guidelines for the treatment of AS.

Statement of when guidelines will be updated

The literature review will be updated in 2017 to inform a revision of the guidelines in 3 years' time.

The guideline

An algorithm for the use of biologics in axSpA, summarizing the recommendations below, is shown in Fig. 2.

Eligibility criteria

These guidelines apply to adult patients with axSpA, including those meeting the modified New York criteria [1] and those with total ankylosis. The diagnosis of axSpA is beyond the scope of these guidelines. However, it should be emphasised that the ASAS classification criteria for axSpA [17] are not intended to be used as diagnostic criteria. While the European Medicines Agency has approved the use of several anti-TNF drugs in patients with nr-axSpA, the US Food and Drug Administration has not allowed the treatment of patients who do not fulfil the modified New York criteria, citing several concerns related to inappropriate diagnosis and treatment [18]. Clinicians should not use biologic drugs in patients who have no objective signs of inflammation, and/or whose symptoms or elevated CRP might be due to conditions other than axSpA, even if they appear to fulfil the ASAS classification criteria. As always, guidelines are not a substitute for clinical judgement. Discussion with an axSpA specialist should be considered before starting treatment in a patient with nr-axSpA and no SIJ bone marrow oedema on MRI.

Assessment of disease and response to treatment

Anti-TNF drugs in AS

Eighteen eligible RCTs were identified that evaluated the efficacy of the five currently available TNF inhibitors (adalimumab, certolizumab, etanercept, golimumab and infliximab) in patients with AS. The main characteristics and outcomes of these trials are shown in Table 2. These trials all had a placebo control arm except for one study with SSZ as a control [19] and one that compared two doses of etanercept [20]. While the trials used a variety

Table 1 System for assessing quality of studies and determining strength of recommendation

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate possibility that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies (e.g. case reports, case series)
4	Expert opinion
Strength of recommendation	
A	Directly based on level 1 evidence
B	Level 2 evidence or extrapolation from level 1
C	Level 3 evidence or extrapolation from level 1 or 2
D	Level 4 evidence or extrapolation from level 2 or 3

Adapted from A new system for grading recommendations in evidence based guidelines. Harbour R, Miller J. 323:334, BMJ 2001 with permission from BMJ Publishing Group Limited. RCT: randomized controlled trial.

of definitions of active disease, 10 of the 16 placebo-controlled studies used the BASDAI [and spinal pain visual analogue scale (VAS) in most] $\geqslant$4 as inclusion criteria (see Table 2). This definition of active disease was used in the seminal phase III AS studies for all of the TNF inhibitors, apart from etanercept [21].

Similarly, the studies used a variety of primary efficacy end points and time points. The inclusion criteria for eight studies also required the presence of active disease despite treatment with standard therapy (NSAIDs), due to either inadequate response or intolerance.

Ten of the 16 placebo-controlled RCTs, including all the seminal phase III studies, used the ASAS20 response rate as the primary efficacy outcome, with the time scale varying between 12 and 24 weeks. The ASAS20 response rate defines the proportion of patients achieving an improvement $\geqslant$20% and $\geqslant$1 U compared with baseline in three or more of the following four domains: patient's global assessment of disease activity, patient's assessment of pain, function (represented by the BASFI) and inflammation (represented by the mean of BASDAI questions 5 and 6 relating to morning stiffness), with no deterioration (worsening $\geqslant$20% or 1 U) in the remaining domain [22]. All of the placebo-controlled trials achieved the primary efficacy end point except for one early study where the primary end point (BASDAI) was assessed 8 weeks after the last infusion of infliximab [23]. The RCTs also demonstrated efficacy of the TNF inhibitors for a variety of other secondary clinical and patient-reported outcomes. A meta-analysis of TNF inhibitors (no certolizumab studies were included) reported that patients treated with anti-TNF agents were more likely to display an ASAS20 response after 12–14 weeks [relative risk (RR) 2.21 (95% CI 1.91, 2.56)] and 24 weeks [RR 2.68 (95% CI 2.06, 3.48)] compared with controls, which was also true for several other efficacy outcomes [24]. An earlier systematic literature review estimated that treatment effect sizes for anti-TNF agents *vs* placebo ranged between 0.34 (95% CI 0.08, 0.6) and 1.5 (95% CI 0.45, 2.5) for the BASDAI, with numbers needed to treat of 2.3–2.7 for ASAS20 responses [25].

While several early RCTs excluded patients with advanced or complete spinal fusion, one study specifically evaluated the efficacy of etanercept in patients with advanced radiographic spinal disease [26]. Improvement in the BASDAI at 12 weeks, the primary end point, was significantly greater in the etanercept group compared with placebo. ASAS20 and ASAS40 responses were similar to those seen in trials for patients without advanced spinal disease. Therefore the presence of vertebral or SIJ fusion should not preclude the use of anti-TNF therapy.

Biosimilar drugs in AS

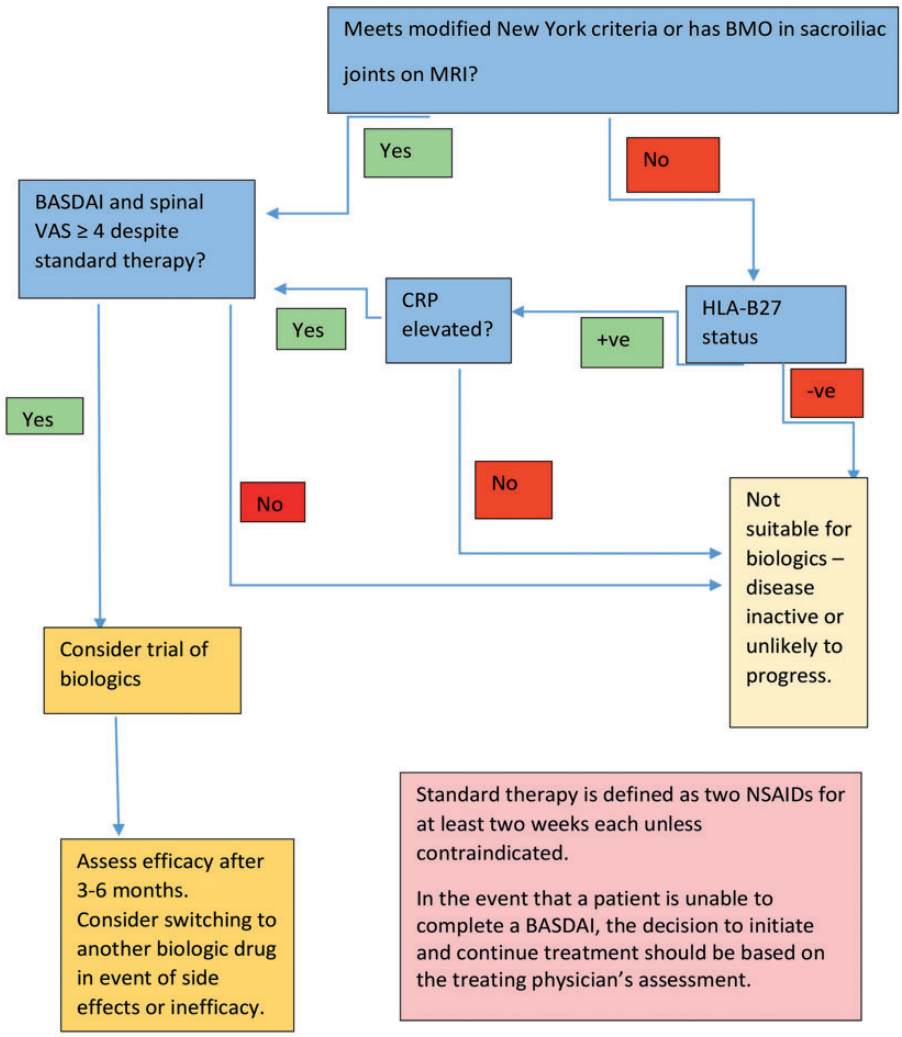
The PLANETAS study was the only RCT of an anti-TNF biosimilar in AS [27]. Patients with AS were randomised to receive either CT-P13 (biosimilar of infliximab; Inflectra or Remsima) or innovator Remicade (infliximab). The regulators require biosimilars to demonstrate proof of similarity of effect, but not *de novo* efficacy. The comparable efficacy of CT-P13 with infliximab had already been demonstrated for RA in the PLANETRA study [28] and is therefore not required for AS due to indication extrapolation (meaning the biosimilar license applies to all the same indications as the innovator biologic, without requiring separate RCTs for each indication). The primary outcome in the PLANETAS study was pharmacokinetic equivalence at steady state, with no statistically significant differences in the secondary clinical outcomes at week 14 or 30 (week 14 ASAS20 62.6% for CT-P13 and 70.5% for Remicade). An indirect meta-analysis reported similar efficacy of the infliximab biosimilar compared with the other TNF inhibitors [29].

The BSR, in its position statement on biosimilars [30], recommends that all patients starting on or switching to a biosimilar drug should be registered with the BSR Biologic Register and that the decision to prescribe a biosimilar should be made primarily on clinical and not cost grounds. In particular, there is no evidence from clinical trials in axSpA to support switching patients who have responded to an innovator biologic to an anti-TNF biosimilar, and such decisions should be made for clinical reasons and on a case-by-case basis.

Other biologic drugs in AS

No non-anti-TNF biologic can currently be recommended for the treatment of AS. When the literature review period

Fig. 2 Treatment algorithm for biologic therapy in axSpA



BMO: bone marrow oedema; VAS: visual analogue scale.

ended in June 2014, either efficacy had not been established in a controlled trial or potential agents were not licensed for this indication. Several new biologic and small molecule inhibitor agents are currently undergoing evaluation and may become available in the near future. A single proof-of-concept study of secukinumab (anti-IL-17A mAb) in AS was identified that suggested a 99.8% probability that secukinumab is superior to placebo based on the ASAS20 at 6 weeks [31]. Further studies have been published subsequently [32]. Although secukinumab is not currently recommended for AS, it has recently been licensed for this indication and we anticipate separate guidance on its use will be issued in due course. A single phase II study of apremilast, a small molecule oral phosphodiesterase 4 inhibitor, in AS failed to reach its primary outcome (change in the BASDAI at week 12), although the clinical results and biomarkers suggest it may be effective for AS [33]. Apremilast is not recommended for AS.

Anti-TNF drugs in nr-axSpA

Six eligible studies examined the efficacy of anti-TNF therapy in patients with nr-axSpA [34–39] (Table 2), although at present only etanercept, adalimumab and certolizumab are licensed for this indication. The trial designs were heterogeneous. Of the studies, only two specifically excluded patients with AS. In the others, the proportion of patients with radiographic sacroiliitis ranged from 12 to 57.5%, although Landewe *et al*. [35] found no significant difference in treatment effect with certolizumab between the AS and nr-axSpA groups.

The two studies excluding AS patients were also the only studies in which active MRI inflammation was not a prerequisite. In Haibel *et al*. [38], eligibility required either inflammation on MRI or HLA-B27 positivity. The majority (55%) of the intervention group had bone marrow oedema in the spine or SIJ on MRI, but neither inflammation in these areas nor HLA-B27 were predictive of a major clinical response. In Sieper *et al*.'s ABILITY-1 study [39], only

Table 2 Summary of efficacy studies of biologic drugs in AS and nr-axSpA found to be of high or acceptable quality

RCTs of anti-TNF drugs in AS						Inclusion criteria for study						
Author [ref]	Intervention	Dose	Comparator	Active arm, *n*	Comparator arm, *n*	Patients meet mNY criteria	BASDAI ⩾4	NSAID fail inclusion criteria	Duration, weeks	Primary outcome	Primary result (active *vs* comparator)	Other outcomes
van der Heijde *et al.* [40]	Adalimumab	40 mg Q2W	PBO	208	107	Y	Y	Y	12	ASAS20	58.2 *vs* 20.6%	ASAS20 week 24 (66 *vs* 0%); BASDAI50 week 12 (45.2 *vs* 15.9%); ASAS40 week 12 (39.1 *vs* 13.1%)
Hu *et al.* [41]	Adalimumab	40 mg Q2W	PBO	26	20	Y	Y	Y	12	None specified	—	BASDAI, BASFI, ASDAS, MRI and biomarkers
Huang *et al.* [42]	Adalimumab	40 mg Q2W	PBO	229	115	Y (Chinese only)	Y	Y	12	ASAS20	67.2 *vs* 30.4%	ASAS40 (44.5 *vs* 9.6%); ASAS5/6 (55.9 *vs* 12.2%); ASAS PR (21.8 *vs* 3.5%); BASDAI50 (49.8 *vs* 16.5%)
Landewe *et al.* [35]	Certolizumab	200 mg Q2W or 400 mg Q4W	PBO	218	107	AS (178) and nr-axSpA (147)	Y	Y	12	ASAS20	57.7% (Q2W); 63.6 (Q4W) *vs* 38.3%	Results similar in AS and axSpA groups; ASAS40 (43.2%; 48.6 *vs* 17.8%); ASAS PR (23.4%; 24.3 *vs* 3.7%); BASDAI, PROs
Gorman *et al.* [43]	Etanercept	25 mg BIW	PBO	20	20	Y	—	—	16	ASAS20	80 *vs* 20%	—
Brandt *et al.* [44]	Etanercept	25 mg BIW	PBO	14	16	Y	Y	—	6	BASDAI50	57 *vs* 6%	—
Davis *et al.* [45]	Etanercept	25 mg BIW	PBO	138	139	Y	—	—	24	ASAS20	57 *vs* 22%	ASAS20 at 12 weeks (59 *vs* 28%); ASAS50 and 70; BASDAI; acute phase response
Calin *et al.* [46]	Etanercept	25 mg BIW	PBO	45	39	Y	—	—	12	ASAS20	60.0 *vs* 23.1%	ASAS40 (49 *vs* 10%); ASAS70 (24 *vs* 10%); BASDAI
van der Heijde *et al.* [21]	Etanercept	50 mg QW or 25 mg BIW	PBO	305	51	Y	—	—	12	ASAS20	74% (QW); 71 (BIW) *vs* 37%	ASAS40 (58.1%; 53.3 *vs* 21.6%); ASAS 5/6 (70.3%; 72.0 *vs* 27.5%)
Braun *et al.* [19]	Etanercept	50 mg QW	SSZ	379	187	Y	>3	—	16	ASAS20	75.9 *vs* 52.9%	ASAS20 at 12 weeks (70.9 *vs* 52.4%); ASAS40; ASAS5/6; mean BASDAI; BASMI; BASFI; physician and patient's global
Dougados *et al.* [26]	Etanercept	50 mg QW	PBO	39	43	Y + advance disease	Y	Y	12	AUC BASDAI	(−19.8 *vs* −11.0%)	ASAS20 (67 vs 33%); ASAS40 (44 *vs* 23%); BASDAI50 (46 *vs* 23%)

(continued)

Table 2 Continued

RCTs of anti-TNF drugs in AS						Inclusion criteria for study						
Author [ref]	Intervention	Dose	Comparator	Active arm, *n*	Comparator arm, *n*	Patients meet mNY criteria	BASDAI ⩾4	NSAID fail inclusion criteria	Duration, weeks	Primary outcome	Primary result (active *vs* comparator)	Other outcomes
Navarro-Sarabia *et al.* [20]	Etanercept	50 mg BIW	Etanercept 50 mg QW	54	54	Y	Y	Y	12	ASAS20	63 (BIW) *vs* 68.5% (QW)	ASAS40 (both 46%)
Inman *et al.* [47]	Golimumab	50 mg Q4W or 100 mg Q4W	PBO	278	78	Y	Y	Y	14	ASAS20	59.6% (50 mg); 60 (100 mg) *vs* 21.8%	ASAS40 at 24 weeks (44%; 54 *vs* 15%); ASAS20 at 24 weeks (similar to 14 weeks); mean BASDAI, BASFI; others plus PROs
Bao *et al.* [48]	Golimumab	50 mg Q4W	PBO	108	105	Y (Chinese only)	Y	—	14	ASAS20	24.8% *vs* 49.1%	ASAS20 at weeks 24 (22.9 *vs* 50.9%); ASAS40; BASDAI; BASFI; others including PROs
Braun *et al.* [49]	Infliximab	5 mg/kg	PBO	34	35	Y	Y	—	12	BASDAI50	53 *vs* 9%	ASAS20; ASAS50; ASAS PR; fatigue from BASDAI
van den Bosch *et al.* [50]	Infliximab	5 mg/kg	PBO	20	20	ESSG SpA (21 = AS)	—	—	12	Physician's global and patient global	—	BASDAI change for the 21 AS patients = −3.23 *vs* −0.26
Marzo-Ortega *et al.* [23]	Infliximab + MTX	5 mg/kg	PBO + MTX	28	14	Y (+ CRP >10)	—	Y	30	BASDAI	N/S (8 weeks after last infusion)	—
van der Heijde *et al.* [51]	Infliximab	5 mg/kg	PBO	201	78	Y	Y	Y	24	ASAS20	61.2 *vs* 19.2%	ASAS40 (47 *vs* 12%); BASDAI50 (51 *vs* 11%); ASAS5/6; ASASPR
Pathan *et al.* [33]	Apremilast	30 mg bid	PBO	17	19	Y	?	—	12	Change in BASDAI	N/S (−1.59 *vs* −0.77)	ASAS20 (35.3 *vs* 15.8%); BASMI; BASFI; bone biomarkers
Park *et al.* [27]	CT-P13 (biosimilar infliximab)	5 mg/kg	Infliximab	125	125	Y	Y	?	N/A	PK equivalence	—	ASAS20 at 14 weeks (62.6 *vs* 70.5%); ASAS40 at 14 weeks (41.7 *vs* 51.8%); ASAS20 and ASAS40 at 30 weeks (no statistically significant difference in clinical response at weeks 14 or 30); BASDAI change; SF-36
Baeten *et al.* [31]	Secukinumab	2 × 10 mg/kg	PBO	24	6	Y	Y	Y	6 (Bayesian)	ASAS20	59 *vs* 24%	(99.8% probability secukinumab superior to PBO)
Haibel *et al.* [38]	Adalimumab	40 mg Q2W	PBO	22	24	All negative	N	N	12	ASAS40	54.5 *vs* 12.5%	BASDAI at 12 weeks ADA 3.8, PBO 5.0 (P = 0.036)
Barkham *et al.* [36]	Infliximab	5 mg/kg	PBO	20	20	12%	Y	N	12	MRI score SIJ and spine	Median change −2 IFX *vs* 0 PBO (P = 0.033)	BASDAI −3.41 IFX *vs* 0.75 PBO (P = 0.033) BASFAI −2.7 IFX *vs* 0.47 PBO (P = 0.004)

(continued)

Table 2 Continued

Author [ref]	RCTs of anti-TNF drugs in AS					Inclusion criteria for study			Duration, weeks	Primary outcome	Primary result (active *vs* comparator)	Other outcomes
	Intervention	Dose	Comparator	Active arm, *n*	Comparator arm, *n*	Patients meet mNY criteria	BASDAI ⩾4	NSAID fail inclusion criteria				
Sieper *et al.* [37]	Infliximab + naproxen		PBO + naproxen	105	51	57.5% positive	Y	N (could be naïve)	28	ASAS partial remission	61.9 *vs* 35.3% ($P = 0.002$)	—
Song *et al.* [34]	Etanercept	25 mg Q2W	SSZ or MTX	40	36	51.3% positive	Y	Y	48	MRI SIJ score	ETN 2.4, SSZ 3.5 ($P = 0.02$)	BASDAI ETN 2.5, SSZ 4.4 ($P = 0.001$) BASFI ETN 2.0, SSZ 3.3 ($P = 0.001$)
Sieper *et al.* [39]	Adalimumab	40 mg q2w	PBO	91	94	All negative	Y	Y	12	ASAS40	36 *vs* 15% ($P < 0.001$)	BASDAI −1.9 ADA *vs* −1.0 PBO ($P = 0.004$) BASFI −1.1 ADA *vs* −0.6 PBO ($P = 0.053$)
Landewe *et al.* [35]	Certolizumab	200 mg Q2W or 200 mg Q4W	PBO	111 and 107	107	54.8% positive	Y	Y	24	ASAS20 weeks 12	57.7% Q2W and 63.6% Q4W *vs* 38.3% ($P < 0.004$)	No difference in treatment effect between AS and nr-axSpA

ASAS: Assessment of SpondyloArthritis international Society; ASAS PR: ASAS partial remission criteria; ASAS20: ASAS 20% response criteria; ASAS40: ASAS 40% response criteria; BIW: twice weekly; ETN: etanercept; IFX: infliximab; mNY: modified New York; MTX: methotrexate; N: no; N/S: not significant; PBO: placebo; PK: pharmacokinetic; PROs: patient reported outcomes; QW: every week; Q2W: every 2 weeks; Q4W: every 4 weeks; SF-36: 36-item Short Form Health Survey; Y: yes.

half of those in the intervention group had ever had SIJ inflammation on MRI, and again this did not affect the proportion meeting the primary outcome measure. The remainder fulfilled the ASAS criteria through the clinical arm. In the other studies, all patients had evidence of inflammation on MRI and most had an elevated CRP at baseline. Based on this evidence, the use of anti-TNF therapy in nr-axSpA patients can only be recommended in the presence of objective signs of inflammation, namely positive SIJ MRI and/or elevated CRP. There is no current high-quality evidence for the use of any other biologic drugs in nr-axSpA.

Radiological and other outcomes with anti-TNF drugs

Short-term MRI data support the efficacy of TNF inhibitors in the treatment of spinal and SIJ inflammatory lesions in axSpA. Evidence for anti-TNF therapy on radiographic disease progression (new bone formation and ankylosis) is currently limited. Large, controlled, longer-term clinical trials are needed to clarify whether these drugs may be disease modifiers.

Data on work participation, presenteeism, absenteeism and productivity relating to the effects of TNF inhibition in AS are limited, mainly as extensions of RCTs. Systematic reviews of the literature show a trend towards benefit from the use of anti-TNF drugs in AS [52], although the data are predominantly from patients with long-standing disease [53, 54]. Health-related quality of life measures improve with all available anti-TNF therapies [55, 56], and studies have shown a reduction in hospital admissions [57]. There are insufficient data to suggest differences in health-related quality of life outcomes between the currently available anti-TNF therapies.

Eligibility for treatment

Before considering anti-TNF therapy, patients should have tried a minimum of two NSAIDs at the maximal tolerated dose (unless contraindicated). Two weeks is sufficient time to see a response, with no further benefit over longer periods of treatment [58].

Current NICE guidelines require patients to have active spinal disease on two separate occasions 12 weeks apart, with the aim of avoiding the overtreatment of patients with a short-lived flare of disease. While patients with axSpA do experience variability in symptom intensity, this fluctuation is less pronounced than the sometimes dramatic flares seen in conditions such as RA. Generalized flares in AS last for an average of 2–3 weeks [59], and a Canadian study assessing 141 patients with AS starting anti-TNF therapy found only 1 patient in whom a second BASDAI (calculated after at least 8 weeks) fell below 4 [60]. An interval of 4 weeks between scores is therefore sufficient and should not delay treatment unduly. However, prescribers should be confident that worsening symptoms, radiological changes and elevated inflammatory markers are due to axSpA and not to other pathology, such as malignancy or infection.

Recommendations for treatment eligibility

(i) Anti-TNF therapy is effective at reducing disease activity and spinal pain in axSpA [level of evidence (LOE) 1+; strength of recommendation A; consensus score 9.6].
(ii) Currently there is insufficient evidence to recommend the use of other biologic agents in axSpA (LOE 1+; strength of recommendation B; consensus score 9.3).
(iii) Patients should be considered for anti-TNF therapy if they have active axSpA (LOE 1+; strength of recommendation B; consensus score 9.6).
(iv) Active disease is defined as a BASDAI and spinal pain VAS $\geqslant 4$ despite standard therapy (LOE 1+; strength of recommendation B; consensus score 8.5).
(v) The BASDAI should be measured on two occasions at least 4 weeks apart (LOE 2+; strength of recommendation C; consensus score 7.2).
(vi) Patients with active disease who do not meet modified New York criteria for AS should also have had a positive MRI and/or elevated CRP (LOE 1+; strength of recommendation B; consensus score 9.3).

Choice of drug

Rationale

In the absence of head-to-head comparisons, systematic reviews [61–63] have shown no statistical difference in efficacy between infliximab, golimumab, etanercept or adalimumab in the treatment of AS (certolizumab data were not included in these comparative reviews). There are insufficient data to comment on relative efficacy in nr-axSpA.

Data on the use of anti-TNF drugs to treat the extra-articular manifestations of axSpA are limited, although a systematic review has shown no statistically significant difference in the rate of uveitis flares in patients with AS treated with infliximab *vs* etanercept [64]. Importantly, not all biologics with efficacy in axSpA are licensed for the treatment of associated conditions. In particular, etanercept has no efficacy in the treatment of IBD [65]. The choice of drug should be a mutual decision between patient and clinician, taking into account factors such as route and frequency of administration and the presence of co-morbidities. Where relevant, advice might be sought from other clinicians managing extra-articular disease.

Recommendation for choice of drug

(i) Extra-articular manifestations and patient choice should be considered when selecting an anti-TNF agent (LOE 4; strength of recommendation D; consensus score 8.9).

Assessing response and monitoring treatment

Rationale

Improvement with anti-TNF drugs is generally seen within the first 6–8 weeks of treatment, and the majority of RCTs assessed primary end points at 12 weeks. However, time to maximal improvement may be >3 months [66] and a proportion of patients will meet the primary end point beyond 12 weeks. In a trial of etanercept *vs* SSZ in AS [19], 75.9% of patients taking etanercept achieved ASAS20 at week 16 compared with 70.9% at week 12. We suggest therefore that a diagnosis of non-response should not be made before 6 months.

Those patients who have responded to treatment should be reviewed every 6 months by their rheumatology team. This allows an evaluation of drug efficacy and tolerability to be made, outcome measure data to be collected and specific issues such as pregnancy and surgery to be discussed with patients. Most patients with axSpA will not be taking concomitant non-biologic DMARDs, so the frequency of any blood monitoring should be determined by local practice and guidelines and the manufacturers' recommendations.

In keeping with international recommendations from the ASAS group, outcome measures should be used that capture the range of outcome domains in axSpA, including pain, physical function, spinal mobility, patient global assessment, peripheral joints and entheses, spinal stiffness and fatigue. Depending on the timescale, it may be appropriate to use spinal X-ray as an outcome, although in clinical practice, when a decision to continue/discontinue treatment is warranted, or in short-term clinical trials, this is unnecessary.

The BASDAI and spinal pain VAS have been used to assess disease activity since publication of the last guidelines, and along with the BASFI and patient global assessment form the ASAS improvement criteria commonly used as a primary outcome measure in clinical trials. While these are subjective measures, they are validated and well understood by clinicians and patients, and at the present time we see no reason to adopt other eligibility criteria for AS patients. In a small minority of patients (e.g. with cognitive or communication difficulties) it will not be possible to assess disease activity using the BASDAI. In this situation, the decision to initiate and continue treatment should be made by the treating physician, taking into account the patient's overall symptoms and preferences.

As a measure of disease activity, the Ankylosing Spondylitis Disease Activity Score (ASDAS) is perhaps not as widely used as the BASDAI, although it includes several of the BASDAI's questions. However, early evidence suggests that it may prove to be a more discriminatory tool in the assessment of disease activity [67]. As ASDAS is a composite index of patient-reported outcomes and objective measures of the acute phase reaction, we would suggest that inflammatory markers should be recorded—preferably CRP. These measures not only have some utility themselves, but can also contribute to computation of the ASDAS. Machado *et al*. [68] found that inflammation on MRI correlated better with CRP than other measures of disease activity, and concluded that the ASDAS, by including both CRP and patient-reported outcomes in its formula, better reflects spinal inflammation than other measures of disease activity.

Recommendations for assessment of response

(i) Initial efficacy response should be assessed following 3–6 months of therapy and responders should

then be reassessed every 6 months (LOE 2+; strength of recommendation D; consensus score 8.6).

(ii) Response is defined as a reduction of the BASDAI and spinal pain VAS by $\geqslant$2 U from baseline (LOE 1+; strength of recommendation B; consensus score 8.3).

(iii) If, because of cognitive or communication difficulties, the BASDAI cannot be used to monitor disease activity, the decision to initiate and continue therapy should be based on the treating clinician's assessment of disease activity (LOE 4; strength of recommendation D; consensus score 9).

Withdrawal of therapy

Rationale

The majority of patients will relapse within 1 year if treatment is withdrawn from those in remission (83% relapse with adalimumab after a mean of 14.7 weeks in nr-axSpA [69]; 77% relapse with etanercept in AS [70]). There is therefore no role for the routine withdrawal of treatment in patients who have achieved remission. Intermittent or on-demand dosing of infliximab has been shown to marginally reduce costs, at the expense of poorer clinical outcomes, and cannot be recommended [71, 72]. There is no high-quality evidence to support the routine use of reduced doses of anti-TNF therapy.

The decision to withdraw treatment because of secondary non-response should not be made after a single raised BASDAI, because symptoms are subject to fluctuation. As noted above, flares last 2–3 weeks on average [59], so a minimum interval of a month before reassessing is suggested.

Recommendations for withdrawal of therapy

(i) In the absence of an initial clinical response by 6 months, or failure to maintain response at two consecutive assessments at least 4 weeks apart, withdrawal of that anti-TNF agent should be considered (LOE 4; strength of recommendation D; consensus score 9.4).

(ii) There is no evidence to support the withdrawal of anti-TNF therapy in treatment responders (LOE 2+; strength of recommendation B; consensus score 9).

Switching drugs

Rationale

At present, AS patients in the UK are only allowed access to one anti-TNF drug, unless they experience an adverse event within 12 weeks of initiating therapy (NICE TA 143). This severely limits the therapeutic options for patients with severe AS, particularly compared with RA, where many more biologic treatment options exist. In effect, clinicians and patients are under pressure to select the correct anti-TNF drug the first time, not knowing whether extra-articular features such as IBD will appear later in the disease course or whether human anti-chimeric antibodies will mediate a suboptimal response after several years of treatment. The current NICE position is also at odds with EULAR [73], ASAS [16] and the Scottish Medicines Consortium, who have not advised against or placed any restriction on sequential anti-TNF therapy in axSpA.

A health economic analysis is outside the scope of these guidelines, so we cannot comment on the cost-effectiveness of switching. Most data on the clinical effectiveness of switching comes from registries or open-label studies without control arms. However, the literature search did identify two studies of sufficiently high quality to be included. In the NOR-DMARD cohort [10], 77 of 514 AS patients treated with an anti-TNF drug switched (30 because of inefficacy, representing $<$6% of the total anti-TNF-treated population). Composite outcome measures were not available for all patients, but the number of patients meeting ASAS40 after 3 months of a second anti-TNF drug was 14/45 (31.1%) *vs* 76/202 (37.6%) for those who had not switched. The only significant difference between switchers (after 3 months of drug 2) and non-switchers (after 3 months of drug 1) was in the proportion achieving BASDAI 50 (28% *vs* 49%, respectively; $P = 0.007$). In the Czech national register ATTRA [11], the response rates of 163 'switch' patients were compared with 1012 patients treated with a first anti-TNF drug. At week 12, the mean BASDAI was 2.4 in non-switchers and 2.6 in switchers ($P = 0.471$). At 2 years, drug survival was 86% in non-switchers, 69% in switchers on subsequent therapy and 28% in switchers on first therapy. In both studies, the numbers of patients who needed to switch because of inefficacy was extremely small and there was no difference in outcome between those switching due to adverse events or inefficacy. No studies have examined switching in nr-axSpA, but there is no reason to assume that outcomes would be significantly different in this group.

Although patients seem to do best if their first anti-TNF drug is both tolerated and effective, there is enough evidence to recommend that patients be allowed to switch to alternative anti-TNF drugs at any point during treatment, whether for reasons of inefficacy or adverse events.

Recommendation for switching drugs

(i) In the event of anti-TNF failure due to inefficacy or adverse event, an alternative anti-TNF agent should be offered if clinically appropriate (LOE 2+; strength of recommendation C; consensus score 9.7).

Safety

Overall

The safety of anti-TNF therapies in axSpA is comparable to other inflammatory joint diseases such as RA. There is little evidence to suggest that safety issues differ hugely with different disease groups, and the 2010 BSR guidelines on the safety of anti-TNF therapies in RA are applicable in axSpA [13]. Pooled RCT data from Gottlieb *et al*. [74] for 2000 patients receiving etanercept (700 with AS) showed a serious infection risk for AS of 3.01/100 patient-

years compared with 3.75 for RA and 3.01 for the whole group. A similar lack of difference according to indication was observed for malignancies, opportunistic infections and mortality.

Reproductive safety

While studies are limited, there is no evidence that anti-TNF therapy adversely affects sperm health in men with axSpA [75]. For issues surrounding female reproductive safety, please see the BSR and BHPR guidelines on prescribing drugs in pregnancy and breastfeeding, part I: standard and biologic DMARDs and corticosteroids (in development).

Vaccination safety

The immune response to vaccination may be impaired in axSpA patients on anti-TNF therapies, although the data are conflicting. Two studies [76, 77] found the response to pandemic influenza vaccination to be unimpaired, one study [78] found the response to pneumococcal vaccination to be impaired only if concomitant MTX was used and one study [79] found the response to pandemic flu vaccination was impaired by mAb anti-TNF therapies.

It is recommended that any one-off vaccinations required by the patient, such as those to prevent pneumonia, should be given before starting treatment. While receiving treatment, appropriate annual vaccinations (such as against influenza) should be given when indicated, although the responses may be attenuated. The shingles (herpes zoster) vaccine (Zostavax) contains live attenuated virus and therefore is not recommended for patients receiving anti-TNF drugs [80].

Tuberculosis (TB)

The risk of TB with anti-TNF therapies in axSpA appears similar to that seen in RA. The risk of TB was 561/100 000 patient-years in an anti-TNF-exposed Korean retrospective cohort of 354 AS patients [81] compared with 69.8/100 000 patient-years in the general population, a similar increase in relative risk to that seen for anti-TNF-treated patients with RA in the BSR Biologics Register (100/100 000 patient-years for all anti-TNF therapies compared with 12/100 000 patient-years in the general population) [82]. It appears that the risk of TB is increased in anti-TNF-treated patients regardless of the indication.

It is therefore recommended that the same screening and prophylaxis for TB carried out prior to initiating anti-TNF therapy in any patient with inflammatory arthritis should be carried out for patients with axSpA, with appropriate vigilance to detect reactivation of TB on treatment should this occur.

Uveitis

Longer-term studies are needed to assess the effect of anti-TNF therapies on the risk of uveitis in axSpA. A prospective study in 2008 with only 19 patients [83] suggested that mAb anti-TNF therapies decreased uveitis flares while etanercept increased them. However, a much larger subsequent study using pooled RCT data from eight trials with 1323 subjects [84] comparing the incidence of uveitis in patients on etanercept (8.6/100 patient-years) *vs* placebo (19.3/100 patient-years) found a beneficial effect for etanercept on uveitis. This study did not compare anti-TNF therapies, and longer-term studies are needed to address the risk of uveitis in axSpA patients treated with different anti-TNF therapies.

Applicability and utility

Barriers to implementation

There are two important differences between these guidelines and the current UK practice determined by NICE, namely the recommendation that treatment be extended to patients with nr-axSpA and objective evidence of inflammation and the recommendation that sequential anti-TNF therapy be permitted. NICE guidance is currently under review, and it may be that similar changes are adopted. However, if this does not occur, then it is unlikely that clinicians (at least outside Scotland) will be able to implement the BSR recommendations in full.

Mechanism for audit of the guidelines

An audit pro forma to assess compliance with these recommendations is available on the BSR website. It is suggested that this be applied to consecutive patients with axSpA attending the clinic, not just those prescribed anti-TNF drugs, as appropriate access to therapy is one standard to be measured.

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Appendix 1
Structured questions

What is the efficacy of biologics in axial SpA (radiographic and non-radiographic)?

Is there evidence for a difference in efficacy and safety between different drugs?

What is the evidence for switching biologics?

Is there evidence on withdrawing biologics?

Evidence for intermittent use of biologics?

Evidence for changing dose?

What are the best predictors of response to treatment?

Is there a difference in efficacy when patients are treated early *vs* late in disease course?

What are the eligibility criteria for biologics?

What outcome measures should be used?

How do we define remission?

Do biologics affect radiographic outcome?

Do biologics affect extra-articular features of SpA?

Do biologics have an effect on work productivity/absenteeism?

Do biologics affect utilization of health care?

Are biologics associated with an increased risk of infection (bacterial, fungal, viral), malignancy, immunogenicity, neurological disease or other side effects?

Are biologics safe around the time of conception (male and female), during pregnancy and during lactation?

Are biologics safe to use in patients with viral hepatitis or HIV?