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

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## Scope and purpose

### Background

Axial spondyloarthritis (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 inflammatory bowel disease. Individuals with axSpA experience significant pain, stiffness and lack of function which translates into important health-economic costs and increased mortality.

Axial SpA can be classified into two subgroups: radiographic axSpA, commonly referred to as ankylosing spondylitis (AS) and non-radiographic axial SpA (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 approximately 12% every 2 years [2], although some patients with nr-axSpA never develop AS. Disease progression is predicted most strongly 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 non-steroidal anti-inflammatory drugs (NSAIDs) may slow the development of radiographic change[4], standard treatment is essentially symptomatic. In contrast to peripheral arthritis, disease modifying anti-rheumatic drugs (DMARDs) have no effect on symptoms or progression of axial disease[5,6].

### **Need for updated guideline**

Several major developments have occurred since the publication of the previous BSR guidelines[7], necessitating a revision. Firstly, 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 guideline**

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 spondyloarthritis and juvenile SpA are outside the scope of these guidelines, and readers are referred to the BSR 2012 guidelines for the management of psoriatic arthritis[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 (NASS). 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 L2**

The evidence for these guidelines is based on a systematic literature search of Medline, EMBASE and the Cochrane library up to 30<sup>th</sup> June 2014. The working group defined the terms of the search using a Patient Intervention Comparison Outcome (PICO) 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 the appendix) 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 orenzia 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, utilisation of healthcare (all categorised as ‘efficacy’ in figure 1),and side effects, vaccine safety, reproductive safety and safety in patients with viral hepatitis or HIV (grouped as ‘safety’ in figure 1). The search terms and outcomes of interest were agreed by the working group in advance of the literature search.

For efficacy outcomes, only high-quality meta-analyses, systematic reviews or RCTs were considered, unless no other data was 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 two years old were accepted unless the same data had been subsequently published.

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, RCP, 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 the European League Against Rheumatism (EULAR) produced updated guidelines in 2010 which included the treatment of non-radiographic disease[15]. 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 three years' time.

## The guideline

An algorithm for the use of biologics in axSpA, summarising the recommendations below, is shown in figure 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[16] are not intended to be used as diagnostic criteria. While the European Medicines Agency (EMA) has approved the use of several anti-TNF drugs in patients with nr-axSpA, the US Food and Drug Administration (FDA) 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[17]. Clinicians should not use biologic drugs in patients who have no objective signs of inflammation, and/or whose symptoms or raised C-reactive protein (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 sacroiliac joint bone marrow oedema on MRI.

### **Assessment of disease and response to treatment**

#### **Anti-TNF drugs in AS**

Eighteen eligible RCTs were identified which 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 apart from one study with sulfasalazine

as control[18] and one which compared two doses of etanercept[19]. While the trials used a variety of definitions of “active” disease, 10 of the 16 placebo controlled studies used BASDAI (and spinal pain VAS in most)  $\geq 4$  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[20].

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 rates as primary efficacy outcome, with the time scale varying between 12-24 weeks. The ASAS20 response rate defines the proportion of patients achieving an improvement of  $\geq 20\%$  and  $\geq 1$  unit compared with baseline in  $\geq 3$  of the following 4 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 of  $\geq 20\%$  or 1 unit) in the remaining domain[21]. All of the placebo-controlled trials achieved the primary efficacy end-point, apart from one early study where the primary end-point (BASDAI) was assessed 8 weeks after the last infusion of infliximab[22]. 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 to 14 weeks (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[23]. An earlier systematic literature review estimated that treatment effect sizes for anti-TNF agents versus placebo varied between 0.34 (95%CI:0.08-0.6) and 1.5 (95%CI:0.45-2.5) for BASDAI, with numbers needed to treat of 2.3-2.7 for ASAS20 responses[24].

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[25]. Improvement in 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. The presence of vertebral or sacroiliac joint fusion should not therefore 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 [26]. 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 [27], 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 to the other TNF inhibitors[28].

The BSR in its position statement on biosimilars[29] recommends that all patients starting on or switching to a biosimilar drug should be registered with the BSR Biologic Register (BSRBR), 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 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-IL17A monoclonal antibody) in AS was identified, which suggested a 99.8% probability that secukinumab is superior to placebo based on the ASAS20 at 6 weeks[30]. Further studies have been published subsequently[31]. 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 BASDAI at week 12), although the clinical results and biomarkers suggest it may be effective for AS[32]. 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 [33–38] (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%, though Landewe et al 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, 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 sacroiliac joints 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 only 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 scan and most had an elevated CRP at baseline in addition. 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 sacroiliac joint MRI and/or raised 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 sacroiliac joint 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 to extensions of RCTs. Systematic reviews of the literature show a trend towards benefit from the use of anti-TNF drugs in AS[39] although the data are predominantly from patients with longstanding disease[40,41]. Health-

related quality of life (HRQOL) measures improve with all available anti-TNF therapies[42,43] and studies have shown a reduction in hospital admissions[44]. There are insufficient data to suggest differences in HRQOL outcomes between the currently available anti-TNF therapies.

### **Eligibility for treatment**

Before considering anti-TNF therapy, patients should have tried a minimum of two non-steroidal anti-inflammatory drugs (NSAIDs) at maximal tolerated dose (unless contra-indicated). Two weeks is sufficient time to see a response, with no further benefit over longer periods of treatment[45].

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 rheumatoid arthritis (RA). Generalised flares in AS last for an average of 2-3 weeks[46], 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[47]. 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 raised 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 by a BASDAI and spinal pain VAS  $\geq 4$  despite standard therapy (LOE 1+; strength of recommendation B; consensus score 8.5).
- (v) 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 raised 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[48–50] 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 versus etanercept[51]. 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 inflammatory bowel disease[52]. 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 comorbidities. 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 endpoints at 12 weeks. However, time to maximal improvement may be longer than three months[53], and a proportion of patients will meet the primary endpoint beyond 12 weeks. In a trial of etanercept vs sulfasalazine in AS[18], 75.9% of patients taking etanercept achieved ASAS20 at week 16 compared to 70.9% at week 12. We suggest therefore that a diagnosis of non-response should not be made before six months.

Those patients who have responded to treatment should be reviewed every six 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.

BASDAI and spinal pain VAS have been used to assess disease activity since the publication of the last guidelines, and along with 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, 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 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 includes several of its individual questions. However, early evidence suggests that it may prove to be a more discriminatory tool in the assessment of disease activity[54]. As ASDAS is a composite index of patient reported outcomes and objective measures of the acute-phase reaction, we would suggest that inflammatory markers are recorded – preferably CRP. These measures not only have some utility themselves, but can also contribute to the computation of the ASDAS. Machado et al[55] 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 to 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 reduction of BASDAI and spinal pain VAS by 2 or more units from baseline (LOE 1+; strength of recommendation B; consensus score 8.3).
- (iii) If, because of cognitive or communication difficulties, 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 one year if treatment is withdrawn from those in remission (83% relapse with adalimumab after mean 14.7 weeks in nr-axSpA[56]; 77% relapse with etanercept in AS[57]). 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[58,59]. 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[46] 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 2 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 in comparison to RA where many more biologic treatment options exist. In effect clinicians and patients are under pressure to select the 'correct' anti-TNF drug first time, not knowing whether extra-articular features such as IBD will appear later in the disease course, or whether human anti-chimeric antibodies (HACAs) will mediate a suboptimal response after several years of

treatment. The current NICE position is also at odds with EULAR[60], ASAS[15] 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%) versus 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 to 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 two 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 for 2000 patients receiving etanercept (700 with AS) showed a serious infection risk for AS of 3.01/100 patient years compared to 3.75 for RA and 3.01 for the whole group[61]. 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 axial SpA[62]. For issues surrounding female reproductive safety, please see the BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding Part I: standard and biologic disease modifying anti-rheumatic drugs 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[63,64] found the response to

pandemic influenza vaccination to be unimpaired, one study[65] found response to pneumococcal vaccination to be impaired only if concomitant methotrexate was used, and one study[66] found response to pandemic flu vaccination was impaired by monoclonal antibody 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[67].

## **TB**

The risk of TB with anti-TNF therapies in axSpA appears similar to that seen in RA. The risk of TB was 561 per 100,000 patient years in an anti-TNF exposed Korean retrospective cohort of 354 AS patients[68] compared to 69.8 per 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 per 100,000 patient years for all anti-TNF therapies compared to 12 per 100,000 patient years in the general population)[69]. 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[70] suggested that monoclonal antibody anti-TNF therapies decreased uveitis flares while etanercept increased them. However, a much larger subsequent study using pooled RCT data from 8 trials with 1,323 subjects[71] 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 guideline**

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

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Trish Cornell was a member of the working group until February 2014 when she took up a post as Rheumatology Nurse Consultant with Abbvie.

## Conflicts of Interest

All members of the Guideline Working Group made declarations of interest in line with the BSR Policy.

LH has received unit funding from Abbvie, MSD, Pfizer and UCB, was sponsored to attend a meeting by MSD, and has received a research grant from Pfizer. NB has received unit funding from Novartis, was sponsored to attend a meeting by Abbvie, and has received speaker fees from Pfizer and UCB. DC was sponsored to attend an international meeting by Pfizer and NASS receives 'hands-off' educational grants from Pfizer, Abbvie, UCB and MSD. GJ has received unit funding from Pfizer and Abbvie, and an honorarium from Abbvie. KM has received unit funding from Abbvie and Pfizer, was sponsored to attend a meeting by MSD and has had a lecture fee and honoraria from Abbvie and honoraria from Novartis and UCB together with educational grants from Abbvie to support the Peninsula Rheumatology Conference for GPs. DMarshall has received honoraria from MSD, Pfizer, Wyeth, UCB, Celgene and Abbvie. HM-O has received unit funding from Pfizer, has been sponsored to attend a meeting by Pfizer, has received honoraria from Abbvie, Celgene, Janssen, MSD, Novartis, Pfizer and UCB and has written a scientific paper in conjunction with Pfizer. DMurphy was sponsored to attend a meeting by MSD, has received honoraria from UCB and Abbvie and sits on an advisory board for Abbvie. CR was sponsored to attend meetings by Abbvie, GSK, MSD, Pfizer and Roche, and received honoraria from UCB. RS is in receipt of research grants from Pfizer and Abbvie, has been sponsored to attend educational meetings by Abbvie and has received honoraria from Abbvie, Pfizer, UCB and MSD. SS has

received unit funding from UCB and Pfizer (research) and Janssen, MSD and Novartis (educational events), has been sponsored to attend meetings by Abbvie, Janssen and MSD, has received speaker fees from Abbvie, Amgen and UCB and advisory board fees from Abbvie, MSD, Pfizer and UCB. LvR has received speaker and advisory board fees, and sponsorship to attend educational meetings, from Abbvie, MSD, Pfizer and UCB. KG has received unit funding from Abbvie, MSD, Pfizer and UCB, has been sponsored to attend meetings by UCB, Abbvie, Pfizer, MSD and has received honoraria from Abbvie, MSD, Pfizer and UCB. The other authors have declared no conflict of interest.

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

<b>Levels of evidence</b>	
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.
<b>Strength of recommendation</b>	
A	Directly based on level 1 evidence
B	Level 2 evidence, or extrapolation from level 1
C	Level 3 evidence, or extrapolation from levels 1 or 2
D	Level 4 evidence, or extrapolation from levels 2 or 3

Adapted from Harbour and Miller BMJ 2001[72]. RCT: randomised controlled trial.

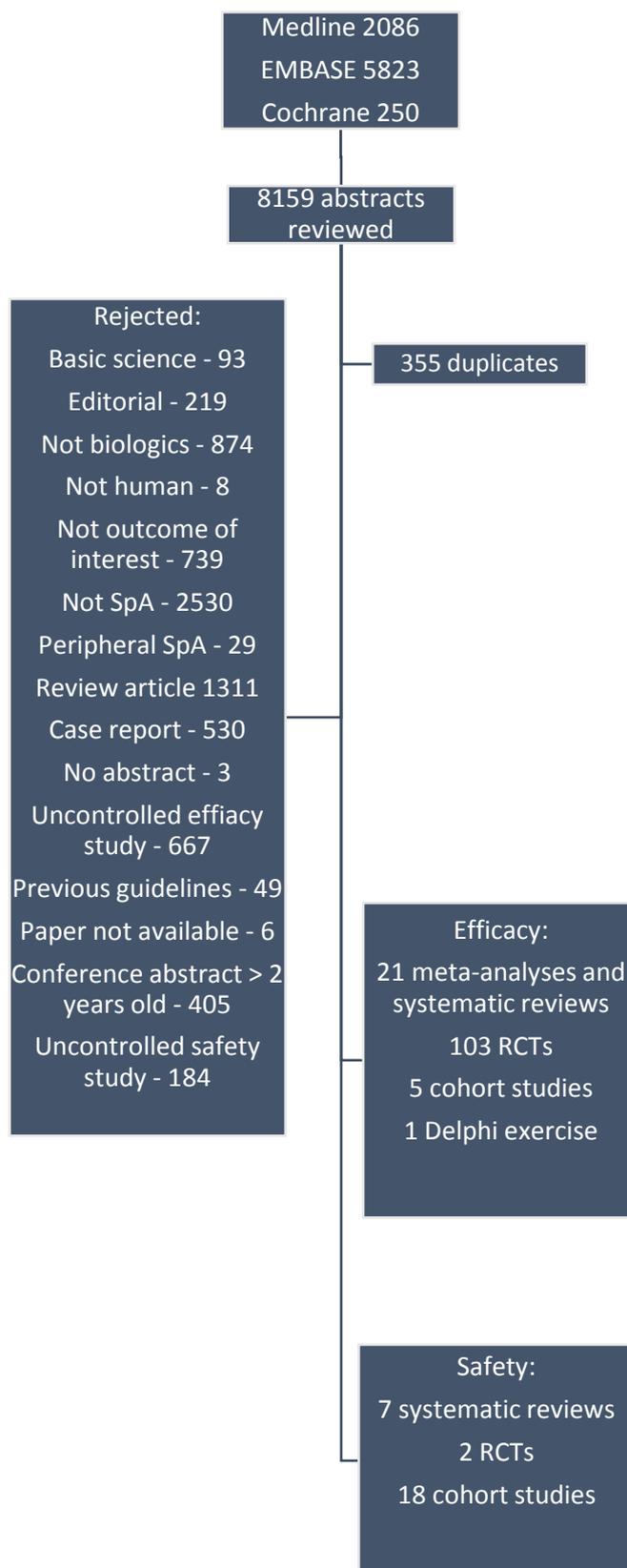


Figure 1 – results of systematic literature review

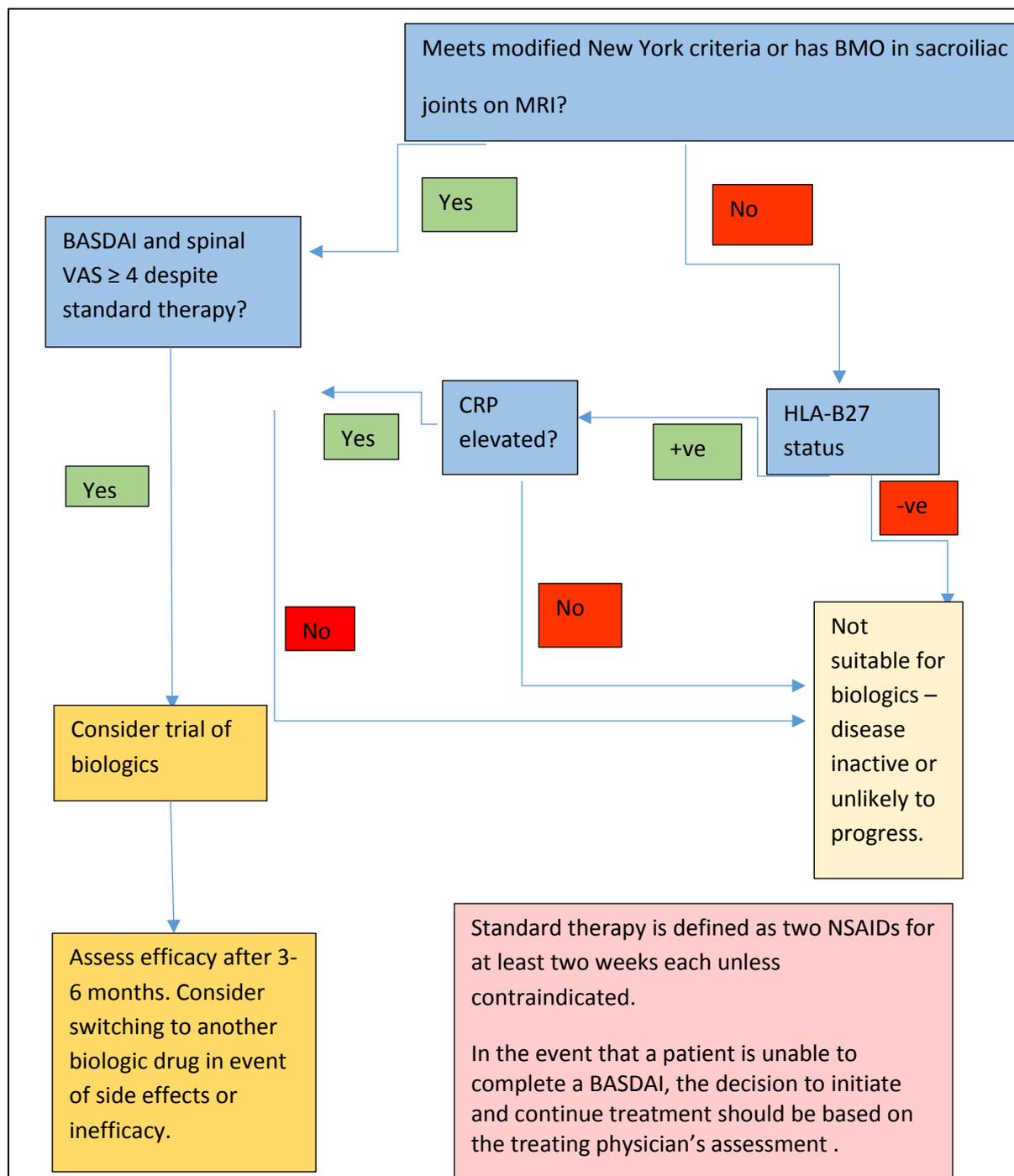


Figure 2 – Treatment algorithm for biologic therapy in axSpA.

BASDAI, Bath AS disease activity score; BMO, bone marrow oedema; CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs; VAS, visual analogue score.

Table 2 – summary of efficacy studies of biologics 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	Number: Active arm	Number: Comparator arm	Pts 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 [73]	Adalimumab	40mg Q2W	PBO	208	107	Y	Y	Y	12	ASAS20	58.2% vs 20.6%	ASAS20 wk 24 (66% v 0%); BASDAI50 wk 12 (45.2 v 15.9%) ASAS40 wk12 (39.1 v 13.1%)	
Hu et al [74]	Adalimumab	40mg Q2W	PBO	26	20	Y	Y	Y	12	None specified	—	BASDAI, BASFI, ASDAS, MRI and biomarkers	
Huang et al [75]	Adalimumab	40mg 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 [34]	Certolizumab	200mg Q2W or 400mg Q4W	PBO	218	107	AS (178) & nrAxSpA (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 [76]	Etanercept	25mg BIW	PBO	20	20	Y	—	—	16	ASAS20	80% vs 20%	-	
Brandt et al [77]	Etanercept	25mg BIW	PBO	14	16	Y	Y	—	6	BASDAI50	57% vs 6%	-	
Davis et al [78]	Etanercept	25mg BIW	PBO	138	139	Y	—	—	24	ASAS20	57% vs 22%	ASAS20 at 12wk (59% vs 28%); ASAS50 & 70; BASDAI; acute phase response	
Calin et al [79]	Etanercept	25mg BIW	PBO	45	39	Y	—	—	12	ASAS20	60.0% vs 23.1%	ASAS40 (49% v 10%); ASAS70 (24% vs 10%); BASDAI	
van der Heijde et al [20]	Etanercept	50mg QW or 25mg 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 [18]	Etanercept	50mg QW	SSZ	379	187	Y	>3	—	16	ASAS20	75.9% vs 52.9%	ASAS20 at 12wk (70.9% vs 52.4%); ASAS40; ASAS5/6; mean BASDAI; BASMI; BASFI; physician and pt global	
Dougados et al [25]	Etanercept	50mg 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%)	

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Navarro-Sarabia et al [19]	Etanercept	50mg BIW	Etanercept 50mg QW	54	54	Y	Y	Y	12	ASAS20	63%(BIW) vs 68.5%(QW)	ASAS40 (both 46%)
Inman et al[80]	Golimumab	50mg Q4W or 100mg Q4W	PBO	278	78	Y	Y	Y	14	ASAS20	59.6%(50mg); 60% (100mg) vs 21.8%	ASAS40 at 24wk (44%; 54% vs 15%); ASAS20 at 24 wk (similar to 14wk); mean BASDAI, BASFI; others plus PROs
Bao et al [81]	Golimumab	50mg Q4W	PBO	108	105	Y (Chinese only)	Y	-	14	ASAS20	24.8% vs 49.1%	ASAS20 at wk 24 (22.9% vs 50.9%); ASAS40; BASDAI; BASFI; others inc. PROs
Braun et al[82]	Infliximab	5mg/kg	PBO	34	35	Y	Y	-	12	BASDAI50	53% vs 9%	ASAS20; ASAS50; ASAS PR; fatigue from BASDAI
Van Den Bosch et al [83]	Infliximab	5mg/kg	PBO	20	20	ESSG SpA (21=AS)	-	-	12	Phys global & Pt global	-	BASDAI change for the 21 AS patients = -3.23 vs -0.26
Marzo-Ortega et al [22]	Infliximab + MTX	5mg/kg	PBO + MTX	28	14	Y (+CRP>10)	-	Y	30	BASDAI	N/S (8wk after last infusion)	
van der Heijde et al [84]	Infliximab	5mg/kg	PBO	201	78	Y	Y	Y	24	ASAS20	61.2% vs 19.2%	ASAS40 (47% v 12%); BASDAI50 (51% vs 11%); ASAS5/6; ASASPR
Pathan et al[32]	Apremilast	30mg bd	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 [26]	CT-P13 (biosimilar infliximab)	5mg/kg	Infliximab	125	125	Y	Y	?	N/A	PK equivalence	-	ASAS20 at 14 wk (62.6% vs 70.5%); ASAS40 at 14 wk (41.7% vs 51.8%); ASAS20 and ASAS40 at 30 wk (no stat sign diff in clinical response at wk 14 or 30); BASDAI change; SF36
Baeten et al[30]	Secukinumab	2 x 10mg/kg	PBO	24	6	Y	Y	Y	6 (Bayesian)	ASAS20	59% vs 24%	(99.8% probability secukinumab superior to PBO)
Haibel et al[37]	Adalimumab	40mg Q2W	PBO	22	24	All -ve	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[35]	Infliximab	5mg/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)
Sieper et al[36]	Infliximab + naproxen		PBO + naproxen	105	51	57.5% +ve	Y	N (could be naïve)	28	ASAS partial remission	61.9% vs 35.3% (p=0.002)	
Song et al [33]	Etanercept	25mg Q2W	SSZ or MTX	40	36	51.3% +ve	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[38]	Adalimumab	40mg q2w	PBO	91	94	All -ve	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)

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Landewe et al [34]	Certolizumab	200mg Q2W or 200mg Q4W	PBO	111 and 107	107	54.8% +ve	Y	Y	24	ASAS20 wk 12	57.7% Q2W and 63.6% Q4W vs 38.3% (p<0.004)	No difference in treatment effect between AS and nr-axSpA
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mNY: modified New York; QW: every week; Q2W: every 2 weeks; Q4W: every 4 weeks; BIW: twice weekly; PBO: placebo; SSZ: sulfasalazine; MTX: methotrexate; Y:Yes ; N:No ; ASAS20: ASAS 20% response criteria; ASAS 40: ASAS 40% response criteria ; ASAS PR: ASAS partial remission criteria ; ETN: etanercept ; N/S: not significant ; SIJ: sacroiliac joint; IFX: infliximab ; PT: patient ;PK: pharmacokinetic; SF36: 36-item Short Form Health Survey;

## Appendix

### 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 utilisation 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?