Guidelines

BSR guidelines for prescribing TNF-α blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology

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Two TNF-blocking drugs are now licensed for the treatment of ankylosing spondylitis (AS) and there is clear evidence of symptomatic efficacy. It is recognized that the instruments for analysing aspects of AS and the outcomes of treatment are imperfect, though they are validated and adequate for the purpose.

This document provides guidance to enable consultant rheumatologists in the UK to balance the demonstrated merits of TNF blockade treatment against the known and unknown potential toxicity.

Background

AS is an inflammatory condition primarily affecting the spine. Onset is most common in the third decade of life, though the disease may remain symptomatic and progressive throughout life. It is part of the family of spondyloarthopathies, which also includes psoriatic arthritis, reactive arthritis and enteropathic arthritis. Undifferentiated forms of spondyloarthopathy, often presenting as mono- or oligoarthritis, are also recognized, as are juvenile forms of spondyloarthopathy, in which the spine is not affected but may become so later. Thus, many individuals with AS also suffer from involvement of the hips, peripheral joints and entheses as well as periodic eye inflammation, inflammatory bowel disease and psoriasis. The treatment of axial and peripheral elements of this disease therefore requires distinct criteria and guidance that is specific for the particular feature.

Symptoms may persist throughout adult life, though some patients experience a diminution of symptoms or even remission of active disease after a period of years. The consequences of active spinal disease, including spinal stiffness or rigidity and increased risk of spinal fracture, are irreversible.

Prevalence and incidence of ankylosing spondylitis

Susceptibility to AS is influenced by genetic factors, particularly HLA-B27 [1, 2]. Thus, the population prevalence of HLA-B27 influences the population prevalence of AS. In Caucasians, the prevalence of AS ranges from 0.05 [3] to 0.23% [4] in adults, men being affected 3–4 times more frequently than women, and in Rochester, Minnesota, an annual incidence rate of 7.3 per 100,000 person years has been calculated [5]. The prevalence of AS and HLA-B27 within different ethnic populations has been reported elsewhere [6].

In a community with a population of 500,000 adults, approximately 500–1000 cases may be expected. Currently some patients with AS do not seek hospital care. Some of these have mild symptoms. Others have ceased to attend hospital clinics because the perceived benefit is small. The availability of new and effective treatment may well influence the number of AS sufferers who seek hospital treatment.

Clinical impact of AS

Individuals with AS suffer pain and disability comparable to that of patients with rheumatoid arthritis [7]. Because the onset of AS is typically earlier than that of rheumatoid arthritis, the impact of these social and economic factors is felt at a younger age.

Up to 50% of patients with adult-onset AS and a higher proportion of those with juvenile onset develop hip arthritis, and many of these will undergo hip replacement surgery [8]; a minority of patients will also require surgery to other joints, especially the knees. Because of heterotopic ossification as well as younger age at the time of surgery, revision of hip replacements is more often necessary than when this procedure is performed for other indications. A minority of patients also undergo spinal surgery because of severe deformity or spinal fracture. Osteoporosis occurs early in disease and contributes to the increased susceptibility to spinal fracture later in life [9, 10].

Life expectancy for people with AS is reduced; the standardized mortality ratio is 1.5 [11, 12]. The excess mortality is mainly accounted for by cardiac valvular disease, amyloidosis and fractures. As a consequence, people with AS bear higher personal insurance costs than the healthy population.
Economic and social impact of AS

Employment

The impact of AS on employment status is significant [7]. In a Dutch study, overall participation in the labour force was 54.2% for the AS cohort, a significant reduction of 11% compared with the general population of the same working age [13]. More than three-quarters of patients with AS who had stopped working were officially recognized as work-disabled.

Approximately one-third of individuals with AS give up work prematurely on health grounds, and an additional 15% suffer constraints within work, including reduction in hours worked and a change of job, as a result of the disease. Work disability is associated with being older, longer duration of disease, lower educational standards, comorbidity, greater physical impairment, pain, fatigue, stiffness, anxious and depressed mood, and lower self-esteem [14].

Health economics

AS carries a significant economic burden, arising from the direct costs of medical care and disability care, and from the indirect costs associated with loss of earnings and reduced productivity.

A prospective longitudinal study of 241 patients with AS [15] estimated annual direct costs (hospitalization, medication, diagnostic tests, ambulatory care visits, assistive devices, travel, paid household help and other treatments) and annual indirect costs (work days missed or, for retirees, days of limited activity). Patients had a mean duration of disease of 20 yr. All patients were assessed for 1 yr, with a subset of 111 patients followed up for 5 yr. Functional disability was measured using the Health Assessment Questionnaire disability index, modified for spondyloarthropathies (HAQ-S). The HAQ-S is a 25-question self-report instrument that asks respondents to assess functional difficulty in 10 areas (dressing, arising, eating, walking, hygiene, reaching, gripping, errands and chores, bending, and driving). The range for each question is from 0 (no difficulty) to 3 (unable to do) and the scores are averaged to produce the HAQ-S (range 0–3).

In the 1-yr follow up, annual total costs averaged US$6720, direct costs contributing 26% of total costs. These figures were similar in the 5-yr cohort. In contrast, studies of the direct and indirect costs of rheumatoid arthritis have suggested that indirect costs are comparable to or lower than direct costs [16, 17]. The larger contribution of indirect costs in AS may reflect the younger age of patients, who may experience work disability for a longer proportion of their working years.

Functional disability was the most important indicator of high total costs and direct costs among these patients. In the 1-yr study, the risks of having high total costs (>US$10 000/yr) increased by a factor of 3 with each 1-point increase in the HAQ-S score. Results were similar in the 5-yr follow up cohort, where the likelihood of high costs (>US$50 000 over 5 yr) was increased by >6 with each 1-point increase in HAQ-S. The authors concluded that interventions that reduce functional disability would be anticipated to be the most effective means of decreasing the costs of AS.

Quality of life

Quality of life has been shown to be adversely affected by AS [18]. The most prevalent quality of life issues related to stiffness (90%), pain (83%), fatigue (62%), poor sleep (54%), concerns about appearance (51%), worry about the future (50%) and medication side-effects (41%).

Studies using the SF-36 (SF-36 Health Survey: Medical Outcomes Trust Inc.) showed that quality of life for AS sufferers was poor, especially in the physical component, figures being worse than some published data for rheumatoid arthritis and even for some cancers [19]. This is also reflected in poor AS-specific quality of life assessment, ASQoL [20].

Conventional treatment for AS

Traditionally, treatment of AS has been directed to relieving pain and stiffness in an attempt to preserve mobility and maintain function. Regular physiotherapy and the use of non-steroidal anti-inflammatory agents (NSAIDs) form the mainstay of treatment. NSAIDs have a quick symptomatic effect, providing in most cases rapid improvement within 48 h after intake and leading to rapid relapse after their discontinuation [21]. This is true to the extent that it has been suggested that, for patients with back pain, the probability of suffering from AS is as low as 3% if there is a failure to respond to NSAIDs [22]. There is, however, no clear indication that their long-term use alters the structural progression of the disease. This, together with the known risk of side-effects (mainly gastrointestinal), has translated into these drugs being used in the majority of patients for clinical relapses rather than as a continuous therapy. The advent of the new cyclooxygenase 2 (COX-2)-specific inhibitors, thought to be as efficacious as conventional NSAIDs [23], may challenge this view.

Instruments for the diagnosis and assessment of AS

The diagnosis of AS is made according to the modified New York criteria [24].

The most widely used measure of the inflammatory activity of AS is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [25]. This simple instrument is patient-completed, sensitive to change over 3 weeks, and has been validated. Some studies have used the two BASDAI spinal stiffness scores as measures of spinal inflammation. Several investigators have included a visual analogue score (VAS) of spinal pain within the last week as a measure of active disease, as the BASDAI does not specify this as a single criterion. Since measures of the acute-phase response are not indicative of the activity of spinal disease, these have not been included in this guideline.

Response to treatment has been gauged primarily by two measures in clinical trials. The reduction in the BASDAI has been shown to be simple and sensitive. Fifty per cent reduction in the BASDAI (BASDAI 50) has been suggested as an appropriate treatment outcome by the Assessments in Ankylosing Spondylitis (ASAS) Working Group. They have also recommended that significant clinical benefit is indicated by reduction of the BASDAI by 50% or a fall of 2 units [26]. Earlier deliberations of the ASAS working group concluded that a response to treatment should be assessed according to a composite score, including VAS scales reflecting pain, inflammation, well-being and function [27]. Improvement in three modalities by 20% or more, without deterioration in the fourth modality, constitutes an ASAS 20 response. Improvements of 50 and 70% in three modalities constitute ASAS 50 and 70 responses, respectively. Current clinical studies indicate comparable performance of the ASAS combined score and the BASDAI 50 or a fall of ≥2 units in assessing response to treatment.

Expert opinion has been recommended by the ASAS group as part of the assessment of appropriateness of TNF blockade...
treatment [27]. Because of lack of transparency and consistency, this has been considered unsuitable for inclusion within a rigorous and transparent guideline.

**Current TNF-blocking agents**

Two TNF-blocking agents are presently licensed in the UK for the treatment of AS: infliximab and etanercept. Others are likely to become available. All trials with etanercept and the majority of trials with infliximab have used treatment regimens as set out in the manufacturers’ recommendations. These advise that treatment with infliximab should be administered by slow intravenous infusion with a loading regimen of 5 mg/kg given at weeks 0, 2 and 6, and maintenance treatment at the same dose given at 6- to 8-weekly intervals. Etanercept is recommended to be given by subcutaneous injection at a dose of 25 mg twice weekly.

**Clinical efficacy of TNF blockade treatment in AS**

**Spinal disease**

Several major studies, summarized in Table 1, attest to the efficacy of infliximab and etanercept (in conjunction with NSAIDs) compared with placebo in the symptomatic treatment of active AS.

By 6–12 weeks, 70–94% of patients achieved the ASAS 20% improvement criteria (ASAS 20) with infliximab [28–31], as did 59–78% of those treated with etanercept [32, 33]. Similar findings were reported by Gorman and colleagues [34], though response criteria differed slightly from those recommended by the ASAS group. Davis et al. [33] demonstrated that around 40% of patients achieved a 50% reduction (ASAS 50) and around 25% achieved a 70% reduction (ASAS 70) within 12 weeks of etanercept treatment, with 17% classified as having achieved ASAS partial remission after 24 weeks. Similarly, Braun et al. [28] demonstrated that around 45% of patients achieved an ASAS 50 response and around 20% achieved an ASAS partial remission at 12 weeks after three doses of infliximab.

Reduction of the BASDAI by 50% was achieved by 55% of patients treated with infliximab [28] and 57% of those receiving etanercept [32] within 6 weeks of treatment. Studies have also demonstrated a significant reduction in the BASDAI compared with baseline values within 2 weeks of treatment with infliximab [29, 35].

Currently, there are no trial data to indicate the need for, or benefit from, combining either agent with a second-line drug, or to indicate the optimum duration of treatment. Response to TNF blockade treatment occurs principally at 6–9 weeks. Cessation of treatment with either agent usually results in recrudescence of symptoms.

**Peripheral arthritis**

These guidelines refer specifically to spinal disease. Further consideration will be given to the treatment of peripheral spondyloarthropathy in due course.

**Peripheral enthesitis**

These guidelines refer specifically to spinal disease. Further consideration will be given to the treatment of peripheral enthesitis in due course.

**Effect on ankylosis**

There are currently no longitudinal data on the prevention of ankylosis after treatment with biologicals. It is postulated that aggressive and persistent suppression of disease activity should lead to prevention of structural damage. MRI is a sensitive imaging technique that allows visualization with good anatomical detail of both the axial and peripheral skeleton.

It is able to detect active inflammation, as shown by bone oedema, as well as chronic change. A number of studies have used MRI to assess disease activity and response to treatment with biologicals [37–39]. Preliminary data suggest that regression of bone marrow oedema is a sensitive sign of improvement of spinal inflammation in AS; however, all these studies reported only on small numbers of patients over a period of time no longer than 6 months. Follow-up data are sparse, and although preliminary results suggest a possible role for MRI as a prognostic predictor, this needs to be confirmed in larger and longer-term studies.

**Related conditions**

**Inflammatory bowel disease.** Patients with Crohn’s disease and spondyloarthropy were treated with infliximab for resistant bowel inflammation. Gastrointestinal symptoms improved and the CRP level fell. In all patients, there was significant improvement in axial and peripheral joint symptoms [41].

**Uveitis.** A retrospective study analysed the effectiveness of etanercept (in 14 patients) or infliximab (two patients) on immunosuppressive resistant eye inflammation when given either for the inflammatory eye disease or associated joint disease [42]. Eight patients had rheumatoid arthritis, three juvenile rheumatoid arthritis, one ankylosing spondylitis and one spondyloarthropy. In three patients, there was no associated systemic disease. In all 12 patients with active articular symptoms and inflammation, there was an improvement, but only six out of 16 patients with ocular inflammation experienced improvement. Five patients developed inflammatory eye disease for the first time whilst taking anti-TNF therapy. It was concluded that TNF inhibitors may benefit certain subgroups of patients with inflammatory eye disease, but more perspective studies were considered necessary.

**Psoriasis.** Several studies have demonstrated beneficial effects of etanercept on psoriasis and psoriatic arthritis. These are cited in the BSR guideline for anti-TNF therapy in psoriatic arthritis [43].

**Effect on bone mineral density (BMD)**

Two studies have examined the effects of anti-TNF treatment on BMD in patients with a spondyloarthropy. One study used infliximab, and either 5 or 3 mg/kg [44] demonstrated a significant increase in bone density at the lumbar spine, total hip and greater trochanter over a 6-month period. There was an increase in the bone formation marker osteocalcin between baseline and week 6 without any corresponding change in a bone resorption marker. The second study examined 10 patients with spondyloarthropy compared with 10 controls with shorter disease duration [45]. Patients were treated with etanercept 25 mg subcutaneously twice weekly. BMD at the lumbar spine and total hip increased in the anti-TNF group compared with the control group treated with NSAIDs and...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Level of evidence and study design</th>
<th>No. of patients and diagnoses</th>
<th>Disease duration</th>
<th>Definition of active disease</th>
<th>Primary response criteria (secondary response criteria)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Ib RCT</td>
<td>70 AS</td>
<td>Mean 16.4 yr treatment/14.9 yr placebo group</td>
<td>BASDAI ≥4/10 Spinal pain VAS ≥4/10</td>
<td>BASDAI 50% reduction (BASFI, BASMI, ASAS 20%, ASAS partial, CRP, SF-36, BASRI, ESR, VAS spinal pain)</td>
<td>5 mg/kg × 3</td>
</tr>
<tr>
<td>35</td>
<td>Ib RCT</td>
<td>40 SpA (19 AS, 18 PsA, 3 uSpA)</td>
<td>Median 6.5 yr Inflammatory spinal pain</td>
<td>Patient global assessment of disease activity VAS</td>
<td>Physicac global assessment of disease activity VAS Patient assessment of pain VAS ESR, CRP</td>
<td>5 mg/kg × 3</td>
</tr>
<tr>
<td>30</td>
<td>Ibb OL</td>
<td>65 AS</td>
<td>Mean 16.4 yr treatment/14.9 yr placebo group</td>
<td>BASDAI ≥4/10 Spinal pain VAS ≥4/10</td>
<td>BASDAI 50% reduction (BASFI, BASMI, ASAS 20%, ASAS partial, CRP, SF-36, BASRI, ESR, VAS Spinal pain)</td>
<td>5 mg/kg every 6 weeks</td>
</tr>
<tr>
<td>29</td>
<td>Ibb OL</td>
<td>50 AS</td>
<td>Median 13 yr BASDAI ≥3/10 CRP ≥15 mg/l</td>
<td>Global assessment of pain GAP VAS 20% reduction (ASAS 20%)</td>
<td>5 mg/kg × 3</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Ibb OL</td>
<td>21 AS</td>
<td>Mean 13.8 yr Expert opinion</td>
<td>BASDAI, BASFI, BASMI, BASG, CRP, ESR, 66 swollen joint count</td>
<td>3 mg/kg × 3 then every 8 weeks</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Ibb OL</td>
<td>19 SpA (10 AS)</td>
<td>Median 15 yr Expert opinion</td>
<td>Patient global assessment of disease activity VAS</td>
<td>Physicac global assessment of disease activity VAS Patient assessment of pain VAS ESR, CRP</td>
<td>5 mg/kg every 14 weeks</td>
</tr>
<tr>
<td>31</td>
<td>Ibb OL</td>
<td>25 AS</td>
<td>Mean 13.5 yr BASDAI ≥3/10 CRP ≥10 mg/l</td>
<td>GAP VAS 20% reduction (GAP 50%, 70% BASDAI, ASAS 20%)</td>
<td>5 mg/kg × 3 then every 8 weeks</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Ib RCT</td>
<td>277 AS</td>
<td>Mean 10.5 yr placebo/10.1 treatment group Morning stiffness ≥3/10 and 2 of – Patient global VAS of disease activity ≥3/10 – Back pain VAS ≥3/10 – BASFI ≥3/10</td>
<td>ASAS 20% (ASAS 50, ASAS 70, ASAS partial remission, BASFI, peripheral joint count, ESR, CRP, physician global assessment VAS, spinal mobility)</td>
<td>25 mg twice weekly</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Ib RCT/OL</td>
<td>40 AS</td>
<td>Mean placebo 12 yr/treatment 15 yr Inflammatory back pain Morning spinal stiffness ≥45 min Patient and physician assessment of disease activity</td>
<td>20% improvement in 3 of the following 5 • duration of morning stiffness • degree of nocturnal spinal pain • BASFI • mean swollen joint score • patient global assessment of disease activity (physician global assessment of disease activity, spinal mobility, Newcastle enthesitis index, peripheral joint tenderness, ESR, CRP)</td>
<td>25 mg twice weekly</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Ib RCT/OL</td>
<td>30 AS</td>
<td>Mean 14.9 yr etanercept group/11.4 placebo group BASDAI ≥4/10 Spinal pain VAS ≥4/10</td>
<td>BASDAI 50% reduction (BASFI, BASMI, ASAS 20%, ASAS partial, CRP, SF-36, BASRI, ESR, VAS spinal pain)</td>
<td>25 mg twice weekly</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Ibb OL</td>
<td>10 SpA (7 AS)</td>
<td>Mean 12 yr Expert opinion</td>
<td>Spinal pain VAS Patient and physician global VAS BASDAI BASFI Swollen and tender joint counts Schober’s test AS quality of life questionnaire</td>
<td>25 mg twice weekly</td>
<td></td>
</tr>
</tbody>
</table>

AS was defined in all studies according to the Modified New York Criteria. SpA was defined in all studies according to the European Spondyloarthropathy Study Group criteria. AS, ankylosing spondylitis; SpA, spondyloarthritis; uSpA, undifferentiated spondyloarthritis; PsA, psoriatic arthritis; VAS, visual analogue scale; RCT, randomised controlled trial; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASG, Bath Ankylosing Spondylitis Global assessment; GAP, Global Assessment of Pain; uSpA, undifferentiated Spondyloarthopathyp.
production by monocytes. Overall inflammatory infiltrate remained unchanged [48]. Neutrophils and CD68+ macrophages were reduced, but the ICAM, PECAM and E-selectin. At week 12, the numbers of neutrophils and CD68+ macrophages were reduced, but the ICAM, PECAM and E-selectin.

**Imaging**

In an open-label study of patients meeting the New York criteria for AS, infliximab 5mg/kg was infused at 0, 2 and 6 weeks [46]. Eight of the 21 patients had MRI imaging both before and after infusion to assess inflammatory change. One patient with a contraindication to MRI was examined with ultrasound. MRI demonstrated an improvement in seven of the eight patients in the imaging cohort; improvement in MRI changes could be seen by 48h.

In the second study, of 10 patients with spondyloarthropathy treated with etanercept 25mg twice weekly for 6 months, MRI scans of the sacroiliac joints, the lumbar spine and affected peripheral joints were performed at baseline and 6 months [38]. A total of 99 enthesial lesions were detected before treatment, of which 86% had regressed or improved at 6 months.

MRI imaging of the spine in patients with ankylosing spondylitis before and after therapy with infliximab has also been assessed using a novel scoring system [47]. Lesions, scored by two radiologists, improved by 40% in the infliximab group compared with 6% in the placebo group, determined using gadolinium enhancement. When determined using STIR sequences, improvement of lesions was seen in 60% of the infliximab group compared with a deterioration in 21% of the placebo group. The chronic lesion score improved by 7% in the infliximab group and worsened by 30% in the placebo group. It was concluded that this technique, using STIR (short TI inversion recovery) and gadolinium enhancement sequences and a scoring system, is useful in assessing acute spinal inflammation; MRI activity scores in the spine are parallel but do not precisely reflect clinical improvement.

**Histological findings**

Synovial biopsies obtained from patients with spondyloarthropathy resistant to conventional treatment at baseline, week 2 and week 12 of a conventional infliximab treatment regime were evaluated histologically and immunochemically. There was a decrease in synovial layer thickness and a reduction in the number of CD55+ synoviocytes at week 12. Vascularity was diminished in the sublining area at week 2, with reduced endothelial expression of VCAM, but not ICAM, PECAM and E-selectin. At week 12, the numbers of neutrophils and CD68+ macrophages were reduced, but the overall inflammatory infiltrate remained unchanged [48]. In another study [49] of patients with ankylosing spondylitis, infliximab treatment down-regulated both interferon γ and TNF-α secretion by T cells, but did not alter cytokine production by monocytes.

**Toxicity**

Table 2 summarizes treatment withdrawals and adverse events in clinical trials of anti-TNF-α in AS undertaken to assess treatment efficacy and/or safety as the primary outcome variables. In publications in which the same cohorts of patients are reported, we considered this information when preparing the table. Of 394 AS patients studied, nine (2.3%) discontinued treatment due to lack of efficacy. Twenty-eight patients (7.1%) were withdrawn because of adverse events. These included three major infections (two cases of tuberculosis, one case of septic osteomyelitis) in infliximab-treated patients and five systemic infliximab-related infusion reactions.

There were no deaths or cases of demyelination reported. Antinuclear antibodies developed in 42 out of 276 patients (15%) in which these data were recorded. No cases of SLE were reported.

**These guidelines**

These guidelines have been drawn up by a working party whose membership and affiliations are recorded in Appendix 1. They have been developed for use by consultant rheumatologists within the UK in the treatment of adults with AS. Guidelines for the use of etanercept in children (under 19 yr of age) with juvenile idiopathic arthritis have also been drawn up (NICE Technology Appraisal Guidance 35, March 2002). These specialists have experience in the management of patients with ankylosing spondylitis and familiarity with the use of TNF-blocking drugs.

These guidelines have been developed in the knowledge of existing guidelines for the use of TNF-blocking drugs in patients with rheumatoid arthritis [50]. Where appropriate, they should be read in conjunction with BSR guidelines relating to the treatment of psoriatic arthritis, and the prevention and management of opportunistic infections, including tuberculosis.

These recommendations are based on available clinical evidence. In addition to clinical trial data, the guideline group was cognizant of expert opinions expressed in published papers [including those listed as 51–53]. It is recognized that, as further evidence becomes available, these guidelines will need to be reviewed and revised periodically.

The use of TNF-blocking drugs in this population must be seen in the context of other available therapies. It is anticipated that these agents will be indicated for some but not all patients, and that for most patients existing modalities of treatment will still be appropriate, either alone or in combination with TNF-blocking drugs.

Effective patient education is an important contributor to the effective use of these guidelines.

These guidelines have been subject to peer review (see Appendix 2) and have been appraised according to the AGREE protocol.

**Treatment guideline**

**Eligibility for treatment with TNF-blocking drugs**

Treatment with TNF blocking agents may be appropriate if:

- The patient’s disease satisfies the modified New York criteria [24]:
  - **Radiological criterion:** Sacroiliitis at least grade 2 bilaterally or grade 3 or 4 unilaterally.
  - **Clinical criteria:** Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.

(a) Limitation of motion of the lumbar spine in both the sagittal and the frontal plane.

(b) Limitation of chest expansion relative to normal values correlated for age and sex.

A definite diagnosis of ankylosing spondylitis requires the radiological criterion and at least one clinical criterion.

(All reasonable measures should be taken to ensure that symptoms are due predominantly to AS and that alternative causes, including spinal fracture, disc disease and fibromyalgia, are excluded.)
Table 2. Treatment withdrawals and adverse events in AS anti TNF-α clinical trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total no. of patients (placebo)</th>
<th>Dosage and regimen</th>
<th>Mean observation period (weeks)</th>
<th>Withdrawals</th>
<th>No. of adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Infliximab</td>
<td></td>
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<td></td>
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<tr>
<td>39</td>
<td>10</td>
<td>5 mg/kg 0, 2, 6 weeks</td>
<td>39</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>29</td>
<td>50</td>
<td>5 mg/kg 0, 2, 6 weeks</td>
<td>24</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>21</td>
<td>3 mg/kg 0, 2, 6 weeks and every 2 months</td>
<td>47.5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>35</td>
<td>5 mg/kg 0, 2, 6 weeks and every 14 weeks</td>
<td>12</td>
<td>4 (0)</td>
<td>0</td>
</tr>
<tr>
<td>37</td>
<td>21</td>
<td>5 mg/kg 0, 2, 6 weeks and every 6 weeks</td>
<td>50</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>40</td>
<td>6</td>
<td>3–5 mg/kg 0, 2, 6 weeks</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>20</td>
<td>5 mg/kg 0, 2, 6 weeks</td>
<td>12</td>
<td>2</td>
<td>0</td>
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<tr>
<td>30*</td>
<td>69</td>
<td>5 mg/kg 0, 2, 6 weeks and every 8 weeks</td>
<td>54</td>
<td>15 (22%)</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>31</td>
<td>25</td>
<td>5 mg/kg 0, 2, 6 weeks and every 8 weeks</td>
<td>52</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Etanercept</td>
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<tr>
<td>34</td>
<td>20</td>
<td>25 mg twice weekly</td>
<td>16</td>
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<tr>
<td>32</td>
<td>16</td>
<td>25 mg twice weekly</td>
<td>30</td>
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<tr>
<td>33</td>
<td>139</td>
<td>25 mg twice weekly</td>
<td>24</td>
<td>12 (19)</td>
<td>1 (3)</td>
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<tr>
<td>TOTAL</td>
<td>394 (230)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>43</td>
<td>9</td>
</tr>
</tbody>
</table>

*aSame patient cohort as reference 28.*
- Ankylosing spondylitis is active. Active spinal disease should be defined as:
  
  (a) BASDAI at least 4 cm.
  
  (b) And spinal pain VAS (last week) at least 4 cm.
  
  (c) Both on two occasions at least 4 weeks apart without any change of treatment.

- Failure of conventional treatment with two or more NSAIDs, each taken sequentially at maximum tolerated/recommended dosage for 4 weeks.

Exclusions from treatment
Exclusions as for rheumatoid arthritis apply. Reference should be made to the individual drug data sheets, but important exclusions include:

- Women who are pregnant or breast-feeding.
- Active significant infection.
- Septic arthritis of a native joint within the last 12 months.
- Septic arthritis of a prosthetic joint within the last 12 months or indefinitely if the joint remains in situ.
- New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure for infliximab.
- Clear history of demyelinating disease.

Criteria for withdrawal of therapy
Development of severe adverse effects (as for rheumatoid arthritis).

- Inefficacy, as indicated by failure of the BASDAI to improve by 50% or to fall by at least 2 units and/or for the spinal pain VAS to reduce by at least 2 units after 3 months of therapy.

Definition of response to treatment
Response to treatment is defined as:

- Reduction of BASDAI to 50% of the pretreatment value or a fall of at least 2 units.
- And reduction of the spinal pain VAS (last one week) by at least 2 cm.

- Assessments of response should be carried out between 6 and 12 weeks after initiation of treatment. If the response criteria are not met, a second assessment should be made at 12 weeks. Treatment should not be stopped because of ineffectiveness within 12 weeks.
- Response criteria should be reviewed at intervals of 3 months.

Failure to maintain the original response leads to repeat assessment after 6 weeks; failure to maintain the response on both occasions leads to cessation or change of treatment.

Treatment regimes
These should be according to the manufacturer's recommendations for the treatment of AS.

- Once a consistent response had been achieved, treatment should be reviewed periodically to assess the need for continued treatment, the dose of drug to be used and the intervals between dosing, in order to ensure that patients receive the minimum effective treatment.

Central registry of data
A biologicals register for patients being prescribed anti-TNF therapies for ankylosing spondylitis does not currently exist. However, the working group recommends that such a register is set up for these patients; the BSR is currently pursuing this. In the meantime, the BSR currently recommends that data collection, including updated dosage, outcome and toxicity information, is conducted at a local level. Adverse incidents/serious side-effects arising whilst on anti-TNF therapy should be notified immediately via the yellow card system.

Review of these guidelines
These guidelines will be reviewed annually.

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Appendix 2. Process of review and appraisal of this draft

Formal comments have been sought by the presentation of a draft document at the Annual Meeting of BSR in April 2004 and from:

- BSR Clinical Affairs Committee members
  Dr Ken Morley (BSR)
  Dr Tom Kennedy (BSR)
- Other interested groups
  British Society for Paediatric and Adolescent Rheumatology: Dr Richard Hull
  BSR Psoriatic Arthritis and TNF blockade Working Group: Dr Neil McHugh
  BSR Rheumatoid Arthritis and TNF Blockade Working Group: Dr Jo Ledingham.

Appendix 3. Declaration of interest statement

The Working Party was set up independently of any input or funding from the manufacturers of the biological therapies for ankylosing spondylitis.

Members of the Working Party were asked to clarify their relationships with the manufacturers of the biological therapies. Members were asked to declare if they, as individuals, had been sponsored to attend scientific or other meetings in the past 24 months or if they had a direct financial stake in the manufacturing companies. They were also asked if their units had received funding from the manufacturers to take part in clinical trials of the new biological therapies. Organizations were asked to declare if they had received sponsorship from manufacturers of the new biological therapies for activities related to the new therapies (either educational or promotional) or for activities not related to the new therapies.

The following replies were received.

- The units in which the following working party members work have received funding from one or more of the manufacturers of therapies for ankylosing spondylitis: K. Gaffney, N. Barkham, H. Marzo-Ortega, R. Sturrock, M. Somerville, A. Keat.
- The following working party members have received funding from pharmaceutical companies involved in producing biological therapies to attend scientific meetings in the past 24 months: N. Barkham, A. Keat, M. Somerville, F. Rogers, H. Marzo-Ortega, A. Bhalla.
- BSR has established a register which is funded by the manufacturers of biological therapies for rheumatoid arthritis; training for rheumatologists in data collection has also been funded by these manufacturers.
- The following working party members have received honoraria from the manufacturers of therapies for ankylosing spondylitis: M. Somerville, S. Paul.
- The following working party members have received funding for taking part in clinical trials of the new biological therapies: M. Somerville, P. Wordsworth.
- No working party members declared a direct financial stake, such as personal shareholding, in companies manufacturing the new biological therapies.

Appendix 4. Other guidelines and documents which should be read in conjunction with this document

- Update of BSR guidelines for prescribing TNF-α blockers in adults with rheumatoid arthritis, including update on tuberculosis screening 2004 [50].
- Guideline for anti-TNF-α therapy in psoriatic arthritis 2004 [43].