BSR Guideline for PrescribingTNFα Blockers in Adults with Ankylosing Spondylitis

Chair of the Guideline Working Group:
Dr Andrew Keat

July 2004

The British Society for Rheumatology
41 Eagle Street London WC1R 4TL
Tel: + 44 (0)20 7242 3313
Fax: + 44 (0)20 7242 3277
Email: bsr@rheumatology.org.uk
WWW: http://www.rheumatology.org.uk

Company Number: 3470316
Registered Charity Number: 1067124

Guidelines for prescribing TNF-α blockers in adults with ankylosing spondylitis

Report of a working party of the British Society for Rheumatology

Two TNF blocking drugs are now licensed for the treatment of ankylosing spondylitis and there is clear evidence of symptomatic efficacy. It is recognised that the instruments for analysing aspects of ankylosing spondylitis 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 United Kingdom to balance the demonstrated merits of TNF blockade treatment against the known and unknown potential toxicity.

BACKGROUND

Ankylosing spondylitis (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 life-long. It is part of the family of spondyloarthropathies which also comprises 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 hips, peripheral joints and peripheral 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)– 0.23% (4) adults, with 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 which is comparable to patients with rheumatoid arthritis (7). Because the onset of AS is typically earlier than that of RA, 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, 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 with a standardised mortality ratio of 1.5 (11,12). The excess mortality is mainly accounted for by cardiac valvular disease, amyloidosis and fractures. In consequence, people with AS bear higher personal insurance costs than the healthy population.

ECONOMIC AND SOCIAL IMPACT OF AS

i. Employment

The impact of AS on employment status is significant. 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 recognised as work disabled. Approximately one-third of individuals with AS give up work prematurely on health grounds whilst an additional 15% suffer constraints within work, including reduction in hours worked and change of job, as a result of the disease. Work disability was associated with being older, longer duration of disease, lower educational standards, co-morbidity, greater physical impairment, pain, fatigue, stiffness, anxious and depressed mood and lower self-esteem (14).

ii. Health economics

Ankylosing spondylitis carries a significant economic burden; arising from both 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 ankylosing spondylitis (15) estimated annual direct costs (hospitalisation, 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 years. All patients were assessed for 1 year, with a subset of 111 patients followed up for 5 years. 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 one-year follow up, annual total costs averaged US$6,720, with direct costs contributing 26% of total costs. These figures were similar in the 5-year cohort. In contrast, studies of the direct and indirect costs of Rheumatoid Arthritis have suggested that indirect costs are comparable, 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 one year study, the risks of having high total costs (>$10,000 per year) increased by a factor of 3 with each one point increase in the HAQ-S score. Results were similar in the 5 year follow up cohort, where the likelihood of high costs (>$50,000 over 5 years) 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.

iii. 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 showed that quality of life for AS sufferers was poor, especially in the physical component, with figures being worse than some published data for RA 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 relieve 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 hours after intake and leading to rapid relapse after their discontinuation (21). So much so, that it has been suggested that in patients with back pain the probability of them 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 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 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 modified New York criteria (24).

The most widely used measure of 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 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 acute phase response are not indicative of 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 of the BASDAI has been shown to be simple and sensitive. 50% reduction in the BASDAI has been recommended by the Assessments in Ankylosing Spondylitis (ASAS) Working Group, who have also recommended that and the sensitivity be enhanced by including “or a fall of 2 units” as evidence of significant benefit (26). Earlier deliberations of the ASAS working group concluded that a response to treatment should be assessed according to a composite score including visual analogue scores (VAS) 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 by 50% and 70% in three modalities constitute ASAS 50 and 70 responses. Current clinical studies indicate comparable performance of the ASAS combined score and the BASDAI 50 or fall by =/> 2 units in assessing response to treatment.

Expert opinion has been recommended by the ADSAS group as a 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 TUMOUR NECROSIS FACTOR (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 manufacturers' recommendations. These advise that treatment with infliximab should be administered by slow intravenous infusion with a loading regimen of 5mg/Kg given at weeks 0, 2 and 6 and maintenance treatment at the same dose given at 6-weekly intervals. Etanercept is recommended to be given by subcutaneous injection at a dose of 25mg twice weekly.

CLINICAL EFFICACY OF TNF BLOCKADE TREATMENT IN AS

i. Spinal disease

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

By 6 to 12 weeks, 70-94% of patients achieved the ASAS 20% improvement criteria (ASAS 20) with infliximab [28,29,30,31] as did 59-78% of those treated with etanercept [32,33,34]. Davis et al [34] 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 3 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 [34] within 6 weeks of treatment. Studies have also demonstrated a significant reduction in the BASDAI compared to baseline values within 2 weeks of treatment [29,35].

Currently, there are no trial data to indicate the need for, or benefit from, combining either agent with another second line drug nor to indicate the optimum duration of treatment. Response to TNF blockade treatment occurs principally at 6 to 9 weeks. Cessation of treatment with either agent usually results in recrudescence of symptoms.

ii. Peripheral arthritis

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

iii. Peripheral enthesitis

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

iv. Effect on ankylosis

There are currently no longitudinal data on prevention of ankylosis after treatment with biologics. 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 visualisation with good anatomical detail of both the axial and peripheral skeleton and 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 biologics (37-39). Preliminary data suggests 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 six 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.

v. Related conditions

Inflammatory Bowel Disease: Patients with Crohn's disease and Spondyloarthropathy were treated with Infliximab for resistant bowel inflammation. Gastrointestinal symptoms improved and the CRP 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 fourteen 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 Spondyloarthropathy. In three patients there was no associated systemic disease. In all twelve patients with active articular symptoms and inflammation there was an improvement but only six out of sixteen patients with ocular inflammation experienced improvement. Five patients developed inflammatory eye disease for the first time whilst taking anti-TNF therapy. It concluded that TNF inhibitors may benefit certain sub groups of patients with inflammatory eye disease, but more perspective studies were necessary.

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

vi. Effect on bone mineral density (BMD)

Two studies have examined the effects of anti-TNF treatment on BMD patients with a spondyloarthropathy. One study used Infliximab either 5mgs per kg or 3mgs per kg (43) demonstrated a significant increase in bone density at the lumbar spine, total hip and greater trochanter over a six month period. There was an increase in the bone formation marker osteocalcin between baseline and week 6 without any corresponding change in bone resorption marker. The second study examined ten patients with spondyloarthropathy compared with ten controlled with shorter disease duration (44). Patients were treated with Etanercept 25mgs subcutaneously twice weekly. BMD at the lumbar spine and total hip increased in the TNF group compared to control group treated with non-steroidal anti-

inflammatory drugs and Sulfasalazine though only the total hip bone density change reached statistical significance compared to baseline.

vii. imaging
In an open label study of patients meeting the New York criteria for ankylosing spondylitis Infliximab 5mgs per kg was infused at 0,2 and 6 weeks (45). Eight of the twenty one patients had MRI imaging both pre- and post- infusion to assess inflammatory change. One patient with a contraindication to MR imaging, was examineded with ultrasound. MR imaging demonstrated an improvement in seven of the eight patients in the imaging cohort; improvement in MRI changes could be seen by 48 hours.

In the second study of ten patients with Spondyloarthropathy treated with Etanercept 25 mg. twice weekly for six months, MRI scans of the sacroiliac joints, the lumbar spine and affected peripheral joints were performed at baseline and six months (38). A total of 99 entheseal lesions were detected pre treatment of which 86% 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 (46). Lesions scored by two radiologists, improved by 40% in the Infliximab group compared to 6% in the placebo group determined using Gd-DTPA. When determined using STIR sequences improvement of lesions was seen in 60% of the Infliximab group compared with a deterioration of 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 and post DTPA sequences and a scoring system, is useful in assessing acute spinal inflammation; MRI activity scores in the spine parallel but do not precisely reflect clinical improvement.

viii. 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 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 number of neutrophils and CD68 positive macophages were reduced but the overall inflammatory infiltrate remained unchanged (47). In another study (48) of patients with ankylosing spondylitis Infliximab treatment down regulated both interferon gamma and TNF alpha secretion by T cells, but did not alter cytokine production by monocytes.

TOXICITY

Table II summarises treatment withdrawals and adverse events in AS anti TNF clinical trials undertaken to assess treatment efficacy and/or safety as the primary outcome variables. In publications where the same cohorts of patients are reported, this information has been considered when preparing the table. Of three hundred and ninety-four AS

patients studied, nine patients (12.3%) discontinued treatment due to lack of efficacy. Twenty-eight patients (7.1%) were withdrawn because of adverse events. These included 3 major infections (2 cases of tuberculosis, one case of septic osteomyelitis) in infliximab-treated patients and 5 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 years of age) with juvenile idiopathic arthritis have also been drawn up (NICE Technology Appraisal Guidance 35, March 2002). These specialists will have experience in the management of patients with ankylosing spondylitis and familiarity with use of TNF blocking drugs.

They have been developed in the knowledge of existing guidelines for the use of TNF blocking drugs in patients with rheumatoid arthritis. 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 [49 – 51]. It is recognised 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

Eligability for treatment with TNF blocking drugs

Treatment with TNF blocking agents may be appropriate if:

- ***The patients' disease satisfies the modified New York criteria (24).***

Modified New York Criteria for a Diagnosis of Ankylosing Spondylitis

Radiologic criterion: Sacroiliitis =/> 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.
Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
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.)

- ***Ankylosing spondyitis is active****:* Active spinal disease should be defined as:
  - BASDAI =/>4 cms
  - ***And*** spinal pain VAS (last week) =/>4cms
  - ***Both*** on 2 occasions at least 4 weeks apart without any change of treatment

- ***Failure of conventional treatment*** *with 2 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*
- *Sepsis 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 (CCF) 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 =/>2 units and/or for the spinal pain VAS to reduce by =/>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 =/ >2 units*
- ***And** reduction of the spinal pain VAS (last one week) by =/>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 3 monthly*
- *Failure to maintain the original response leads to repeat assessment after 6 weeks; failure to maintain response on both occasions leads to cessation or change of treatment.*

Treatment regimes

- *Should be as per 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 biologics 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 and the BSR is currently pursuing this. In the meantime 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

- Will be undertaken annually

Appendices

1. Members and affiliations of the working group
2. Process of review of this draft
3. Declaration of interest statement
4. Other guidelines which should be read in conjunction with this document
5. Supporting references alluded to in the formulation of these guidelines.
6. Tables of clinical trials of TNF blockers in the treatment of AS

Appendix 1. Members and affiliations of the working group

Dr Andrew Keat, Chairman (Consultant Rheumatologist, Northwick Park Hospital, Harrow)
Dr Nick Barkham (Specialist Registrar in Rheumatology, Leeds General Infirmary)
Dr Ashok Bhalla (Consultant Rheumatologist RNHRD, Bath)
Dr Karl Gaffney (Consultant Rheumatologist, Norfolk & Norwich Hospital)
Dr Helena Marzo-Ortega (Specialist Registrar in Rheumatology, Leeds General Infirmary)
Dr Simon Paul (Specialist Registrar in Rheumatology, St Thomas' Hospital, London)
Mr Fergus Rogers, (Director, National Ankylosing Spondylitis Society
Dr Nick Somerton, General Practitioner, Hull
Margaret Somerville (Clinical Reasearch Manager, Department of Rheumatology, Norfolk & Norwich Hospital)
Professor Roger Sturrock (Professor of Rheumatology, University of Glasgow, Consultant Rheumatologist, Glasgow Royal Infirmary)
Professor Paul Wordsworth (Professor of Rheumatology, University of Oxford; Consultant Rheumatologist, Nuffield Orthopaedic Centre, Oxford)

Appendix 2. Process of review and appraisal of this draft.

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

2. BSR Clinical Affairs Committee members
   Dr Ken Morley BSR
   Dr Tom Kennedy BSR

3. 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

The draft was then submitted to appraisal according to the AGREE protocol.

Appendix 3. Declaration of interest statement

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

Members of the Working Party were asked to clarify their relationships with the manufacturers of the biologic 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 biologic therapies. Organisations were asked to declare if they had received sponsorship from manufacturers of the new biologic 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 WP 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 WP members have received funding from pharmaceutical companies involved in producing biologic therapies to attend scientific meetings in the past 24months: 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 WP members have received honoraria from the manufacturers of therapies for Ankylosing Spondylitis: M Somerville, S Paul
- The following WP members have received funding for taking part in clinical trials of the new biologic therapies: M Somerville
- No WP members declared a direct financial stake, such as personal shareholding, in companies manufacturing the new biologic therapies.

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

- Update of BSR guidelines for prescribing TNFa blockers in adults with Rheumatoid Arthritis, including update on TB screening. April 2004
- Guideline for anti-TNFa therapy in Psoriatic Arthritis. April 2004
- Guideline for the use of Etanercept in Juvenile Idiopathic Arthritis. March 2002. (NICE Technology Appraisal Guidance 35, March 2002).

- BPRG prescribing guidelines for the prescription of anti-TNF to children and young people with JIA. BSR. 2003.
- BSR Biologics Register Consultant Baseline Questionnaire: Ankylosing Spondylitis. 2004

Appendix 5. References on which these guidelines are based

1. Brewerton DA, Cafferey M, Hart FD *et al*. Ankylosing spondylitis and HL-A. Lancet 1973 1; 904.

2. Wordsworth P. Genes in the spondyloarthopathies. Rheum Dis Clin N Amer 1998 24;845-843.

3. West HF. The aetiololgy of ankylosing spondylitis Ann Rheum Dis 1949 8;143-148

4. Gomor B, Gyodi E, Bakof L. Distribution of HLA-B27 and ankylosing spondylitis in the Hungarian population. J Rheumatol 1977 4 (suppl 3) 33-35

5. Carbone LD, Cooper C, Michet CJ, Atkinson EJ, O'Fallon WM & Melton LJ. Ankylosing spondylitis in Rochester Minnesota 1935-1989. Arthr Rheum 1992 35;1476-1482

6. Gran JT and Husby G. Ankylosing Spondylitis: prevalence and demography. In J. Klippel and PA Dieppe eds Rheumatology 2nd ed. Mosby London. 6.15.1. 1998

7. Zink A, Braun J, Listing J, Wollenhaupt J. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis: Results from the German rheumatological database. J Rheumatol 2000, 27; 613-622.

8. Sweeney S, Gupta R, Taylor G and Calin A. Total hip arthroplasty in Ankylosing Spondylitis: outcome in 340 patients. J Rheumatol. 2001;28:1862-1866

9. Reid M, Nicoll JJ, Kennedy NS, Smith MA, Tothill P, Newquay G. Bone mass in ankylosing spondylitis. J Rheumatol 1986 13; 932-935.

10. Bessant R, Keat A. How should clinicians manage osteoporosis in ankylosing spondylitis? J Rheumatol 1992 29; 1511-1519

11. Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. Ann Rheum Dis 1993 52; 174-176.

12. Simmonds DPM. Mortality in ankylosing spondylitis. Rheum in Europe 1996 25; 15-16.

13. Chorus AMJ, Boonen A, Miedema HS, van der Linden S. Employment prospectives of patients with ankylosing spondylitis. Ann Rheum Dis 2002 61; 693-699.

14. Barlow JH, Wright CC, Williams B, Keat A. Work disability among people with ankylosing spondylitis. Arthr Rheum 2001 45; 424-429.

15.Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. Arthr Rheum 2002 46; 223-231.

16.Newhall-Perry K, Law NJ, Ramos B, Sterz N, Wong WK, Bulpit KJ *et al*. Direct and indirect costs associated with the onset of seropositive rheumatoid arthritis. J Rheumatol 2000 27; 1156-1163.

17.Cooper MJ. Economic burden of rheumatoid arthritis: A systematic review. Rheumatology 2000 39; 28-33

18. Ward MM. Quality of life in patients with ankylosing spondylitis. Rheum Dis Clin North Am. 1988;24:815-27.

19. Haywood KL. Health outcomes in ankylosing spondylitis: an evaluation of patient-based and anthropometric measures. (Dphil Thesis). York: University of York; 2000, 353p.

20. Doward LC, Spoorenberg A, Cook SA, Whalley D, Heliwell PS, Kay LJ, McKenna SP, Tennant A, van der Heijde D, Chamberlain MA. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-26.

21. Amor B. Dougados M, Mijiyawa M. Criteres de classification des spondylarthropathies. Rev Rhum 1990;57:85-9.

22. Miceli-richard C, Dougados M. NSAIDs in ankylosing spondylitis. Clin Exp Rheumatol 2002;20(Suppl. 28):S65-66.

23. Dougados M, Behier JM, Jolchine I, et al. Efficacy of celecoxib, a cyclooxigenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against conventional non-steroidal anti-inflammatory drugs. Arthritis Rheum 2001;44:180-5.

24. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis; a proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-368

25. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: The Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994 21; 2286-2291.

26. Braun J, Pham T Sieper J van der Linden SJ, Dougados M, van der Heijde D. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Annals of the Rheumatic Diseases. 2003;62:817-824

27. Braun J. Sieper J. Building consensus on nomenclature and disease classification for ankylosing spondylitis: Results and discussion of a questionnaire prepared for the International Workshop on New Treatment Strategies in Ankylosing Spondylitis, Berlin, Germany, 18-19 January 2002. Annals of the Rheumatic Diseases. Vol. 61(SUPPL. 3)(pp iii61-iii67), 2002.

28. Braun J. Brandt J. Listing J. Zink A. Alten R. Golder W. Gromnica-Ihle E. Kellner H. Krause A. Schneider M. Sorensen H. Zeidler H. Thriene W. Sieper J. Treatment of active ankylosing spondylitis with infliximab: A randomised controlled multicentre trial. Lancet. 2002**; 359**:1187-1193.

29. Breban M. Vignon E. Claudepierre P. Devauchelle V. Wendling D. Lespessailles E. Euller-Ziegler L. Sibilia J. Perdriger A. Mezieres M. Alexandre C. Dougados M. Efficacy of infliximab in refractory ankylosing spondylitis: Results of a six-month open-label study. Rheumatology. 2002;**41**:1280-1285.

30. Braun J. Brandt J. Listing J. Zink A. Alten R. Burmester G. Golder W. Gromnica-Ihle E. Kellner H. Schneider M. Sorensen H. Zeidler H. Reddig J. Sieper J. Z. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three month, randomised, placebo-controlled trial. Arhritis Rheum. 2003;48:2224- 2233.

31. Temekonidis TI. Alamanos Y. Nikas SN. Bougias DV. Georgiadis AN. Voulgari PV. Drosos AA. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study. Annals of the Rheumatic Diseases 2003; **62**: 1218 – 1220

32. Brandt J. Khariouzov A. Listing J. Haibel H. Sorensen H. Grassnickel L. Rudwaleit M. Sieper J. Braun J. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis & Rheumatism. Vol. 48(6)(pp 1667-1675), 2003.

33. Gorman JD. Sack KE. Davis Jr JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor a. New England Journal of Medicine. Vol. 346(18)(pp 1349-1356), 2002.

34. Davis JC. Van der Heijde D. Braun J. Dougados M. Cush J. Clegg DO. Kivitz A. Fleischmann R. Inman R. Tsuji W. Recombinant human tumor necrosis factor receptor (Etanercept) for treating ankylosing spondylitis. Arthritis & Rheumatism 2003 48 (11): 3230 – 3236.

35. Van den Bosch F. Kruithof E. Baeten D. Herssens A. de Keyser F. Mielants H. Veys E. Randomised double blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) versus placebo in active spondyloarthropathy. Arthritis and Rheumatism 2002;**46**:755-765

36. Maksymowych WP. Jhangri GS. Lambert RG. Mallon C. Buenviaje H. Pedrycz E. Luongo R. Russell AS. Infliximab in ankylosing spondylitis: A prospective observational

inception cohort analysis of efficacy and safety. Journal of Rheumatology. 2002;**29**:959-965.

37. Kruithof E. Van den Bosch F. Baeten D. Herssens A. De Keyser F. Mielants H. Veys EM. Repeated infusions of infliximab, a chimeric anti-TNFa monoclonal antibody, in patients with active spondyloarthropathy: One year follow up. Annals of the Rheumatic Diseases. 2002;**61:**207-212.

38. Marzo-Ortega H. McGonagle D. O'Connor P. Emery P. Efficacy of etanercept in the treatment of the entheseal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study.[comment]. Arthritis & Rheumatism. 44(9):2112-7, 2001

39. Brandt J. Haibel H. Sieper J. Reddig J. Braun J. Infliximab treatment of severe ankylosing spondylitis: one year follow-up. Arthritis and Rheumatism 2001;**44**:2936 – 2937.

40. Brandt J, Haibel H, Reddig J. Sieper J and Braun J. Successful short term treatment of severe undifferentiated spondyloarthropathy with the anti-tumour necrosis factor alpha monoclonal antibody infliximab. J. Rheumatol. 2002;29:118-122

41. Van den Bosch F, Kruithof E, de Vos M, de Keyser F, Mielants H. Crohn's disease associated with spondyloarthropathy: effect of TNF alpha blockade with infliximab on articular symptoms. Lancet 2000;356:1821-1822

42. Smith JR, Levinson RD, Holland GN, Jabs DA, Robinson MR, Whitcup SM Rosenbaum JT. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Care and Research 2001;45:252-257

43. Allali F. Breban M. Porcher R. Maillefert JF. Dougados M. Roux C. Increase in bone mineral density of patients with spondyloarthropathy treated with anti-tumour necrosis factor alpha. Annals of the Rheumatic Diseases 2003;**62**:347 – 349

44. Marzo-Ortega H. McGonagle D. Haugeberg G. Green MJ. Stewart SP. Emery P. Bone mineral density improvement in spondyloarthropathy after treatment with etanercept. Annals of the Rheumatic Diseases 2003;**62**:1020 – 1021.

45. Stone M. Salonen D. Lax M. Payne U. Lapp V. Inman R. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. Journal of Rheumatology. 28(7):1605-14, 2001

46. Braun J. Baraliakos X. Golder W. Brandt J. Rudwaleit M. Listing J. Bollow M. Sieper J. Van der Heijde D. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: Evaluation of a new scoring system. Arthritis & Rheumatism. Vol. 48(4)(pp 1126-1136), 2003.

47. Baeten D. Kruithof E. Van den Bosch F. Demetter P. Van Damme N. Cuvelier C. De Vos M. Mielants H. Veys EM. De Keyser F. Immunomodulatory effects of anti-tumor necrosis factor alpha therapy on synovium in spondylarthropathy: Histologic findings in eight patients from an open-label pilot study. Arthritis & Rheumatism. Vol. 44(1)(pp 186-195), 2001.

48. Zou J. Rudwaleit M. Brandt J. Thiel A. Braun J. Sieper J. Down-regulation of the nonspecific and antigen-specific T cell cytokine response in ankylosing spondylitis during treatment with infliximab. Arthritis & Rheumatism. Vol. 48(3)(pp 780-790), 2003.

49. Braun J. Sieper J. Breban M. Collantes-Estevez E. Davis J. Inman R. Marzo-Ortega H. Mielants H. Anti-tumour necrosis factor a therapy for ankylosing spondylitis: International experience. Annals of the Rheumatic Diseases. Vol. 61(SUPPL. 3)(pp iii51-iii60), 2002.

50. Stokes DG. Kremer JM. Potential of tumor necrosis factor neutralization strategies in rheumatologic disorders other than rheumatoid arthritis. Seminars in Arthritis & Rheumatism. Vol. 33(1)(pp 1-18), 2003.

51. Maksymowych WP. Inman RD. Gladman D. Thomson G. Stone M. Karsh J. Russell AS. Spondyloarthritis Research Consortium of Canada (SPARCC). Canadian Rheumatology Association Consensus on the use of anti-tumor necrosis factor-alpha directed therapies in the treatment of spondyloarthritis.[comment]. Journal of Rheumatology. 30(6):1356-63, 2003 Jun.

Appendix 6

Table 1. Overview of most relevant clinical trials using anti-tumour necrosis factor α agents in patients with spondylitis.

reference number	Scientific paper	Level of evidence & Study design	Number of patients and diagnoses	Disease duration	Definition of active disease	Primary response criteria (secondary response criteria)	Dosage
	INFLIXIMAB						
28	**Braun J, Lancet 2002**	Ib RCT	70 AS	Mean 16.4 y treatment /14.9 y placebo group	BASDAI ≥ 4/10 Spinal pain VAS ≥4/10	BASDAI 50% reduction (BASFI, BASMI, ASAS 20%, ASAS partial, CRP, SF 36, BASRI, ESR, VAS Spinal pain)	5 mg/kg x 3
34	*Van den Bosch, Arthritis Rheum 2002*	Ib RCT	40 SpA (19 AS, 18 PsA, 3 uSpA)	Median 6.5 y	Inflammatory spinal pain	Patient global assessment of disease activity VAS Physician global assessment of disease activity VAS Patient assessment of pain VAS ESR, CRP	5 mg/kg x 3
30	*Braun J, Arthritis Rheum 2003 (same cohort as paper 4)*	IIb OL	65 AS	Mean 16.4 y treatment /14.9 y placebo group	BASDAI ≥ 4/10 Spinal pain VAS ≥4/10	BASDAI 50% reduction (BASFI, BASMI, ASAS 20%, ASAS partial, CRP, SF 36, BASRI, ESR, VAS Spinal pain)	5 mg/kg ev 6 w
29	*Breban M, Rheumatology 2002*	IIb OL	50 AS	Median 13 y	BASDAI≥3/10 CRP≥15mg/L	Global assessment of pain GAP VAS 20 % reduction (ASAS 20%)	5 mg/kg x 3
36	*Maksymowych W, J Rheumatol 2002*	IIb OL	21 AS	Mean 13.8 y	Expert opinion	BASDAI, BASFI, BASMI, BASG, CRP, ESR, 66 swollen joint count	3 mg/kg x3 followed by ev 8 w
37	*Kruithof E, Ann Rheum Dis 2002 (same cohort as paper 7)*	IIb OL	19 SpA (10 AS)	Median 15 years	Expert opinion	Patient global assessment of disease activity VAS Physician global assessment of disease activity VAS Patient assessment of pain VAS ESR, CRP	5 mg/kg ev 14 w
31	*Temekonidis T, Ann Rheum Dis 2003*	IIb OL	25 AS	Mean 13.5 y	BASDAI≥3/10 CRP≥10mg/L	GAP VAS 20 % reduction (GAP 50%, 70%BASDAI, ASAS 20%)	5 mg/kg x 3 then ev 8 w
	ETANERCEPT						

34	**Davis J, Arthritis Rheum 2003**	Ib RCT	277 AS	Mean 10.5 y 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	ASAS 20% (ASAS 50, ASAS 70, ASAS partial remission, BASFI, peripheral joint count, ESR, CRP, physician global assessment VAS, spinal mobility)	25 mg twice w
33	*Gorman J, N Engl J Med 2002*	Ib RCT/OL	40 AS	Mean placebo 12 y/treatment 15 years	Inflammatory back pain Morning spinal stiffness ≥45 minutes Patient & physician assessment of disease activity	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)	25 mg twice w
32	*Brandt J, Arthritis Rheum 2003*	Ib RCT/OL	30 AS	Mean 14.9 y etanercept group/11.4 placebo group	BASDAI ≥ 4/10 Spinal pain VAS ≥4/10	BASDAI 50% reduction (BASFI, BASMI, ASAS 20%, ASAS partial, CRP, SF 36, BASRI, ESR, VAS Spinal pain)	25 mg twice w
38	*Marzo-Ortega H, Arthritis Rheum 2001*	IIb OL	10 SpA (7 AS)	Mean 12 y	Expert opinion	Spinal pain VAS Patient & physician global VAS BASDAI BASFI Swollen & tender joint counts Schober's test AS quality of life questionnaire	25 mg twice w

NB: AS was defined in all studies following the Modified New York Criteria. SpA was defined in all studies according to the European Spondyloarthropathy Study Group Criteria.
AS – Ankylosing spondylitis, SpA – spondyloarthropathy, uSpA - undifferentiated spondyloarthropathy, PsA - psoriatic arthritis, VAS – visual analogue scale

TABLE II. Treatment withdrawals and adverse events in AS anti TNF clinical trials

BSR working group scientific reference number	Total no of patients (placebo)	Dosage & regimen	Mean Observation period (weeks)	Withdrawals				Number of Adverse events						ANA
				Total	Lack of Efficacy	Adverse events	Other	Total Number	Infections		Treatment reactions		Other	
									Major	Minor	Local	Systemic		
		INFLIXIMAB												
Brandt 2001	39	5mg/Kg 0,2,6 wks	39	4	0	3	1	12	0	9	0	2	1	1
Breban 2002	29	5mg/Kg 0,2,6 wks	24	2	0	2	0	40 pts (80%)	0	25 pts (50%)	0	0	0	0
Maksymowych 2002	36	3 mg/Kg 0,2,6 wks & q 2 mths	47.5	4	1	2	1	Not reported	1	Not reported	0	1	0	0
Braun 2002	28	5 mg/Kg 0,2,6 wks	12	4 (0)	0	3 (0)	1	Not reported	1	12 (18)	0	0	2	0
Kruithof 2002	37	5 mg/Kg 0,2,6 wks & q 14 wks	50	2	2	0	0	19 pts	0	12 events	0	1	0	12 (57 %) (19% DNA)
Brandt 2002	40	3-5 mg/Kg 0,2,6 wks	12	0	0	0	0	2	0	1	0	0	0	0
Van den Bosch 2002	34	5 mg/Kg 0,2,6 wks	12	2	0	2	0	21 (14)	1	6 (6)	0	0	0	4 (2 DNA)
*Braun 2003**	30	5 mg/Kg 0,2,6 wks & q 6 wks	54	15 (22%)	2 (2.9%)	11 (16%)	2	54	***1***	35	0	0	**0**	17 (25%) 4 DNA
Temekonidis 2003	31	5 mg/Kg 0,2,6 wks & q 8 wks	52	2	1	1	0	12	0	8	2	1	0	6 (24%)
		ETANERCEPT												
Gorman 2002	33	25 mg twice weekly	16	0	0	0	0	17 (13)	0	10 (12)	5 (1)	0	0	2 (2)
Brandt 2003	32	25 mg twice weekly	30	0	0	0	0	Not reported	0	6 (6)	2 (0)	0	0	Not recorded
Davis 2003	34	25 mg twice weekly	24	12 (19)	3 (13)	7 (1)	2 (5)	185 (125)	0 (0)	28 (16)	41 (13)	0	0	Not recorded
TOTAL	**394 (230)**			**43**	**9**	**28**	**6**		**3**			**5**		

**same patient cohort as reference 28*