

## EXTENDED REPORT

# International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis

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*Ann Rheum Dis* 2003;62:817–824

**Objective:** To obtain an international consensus about the use of anti-tumour necrosis factor  $\alpha$  (anti-TNF $\alpha$ ) for treating patients with ankylosing spondylitis (AS).

**Methods:** These recommendations were developed by a review of published reports in combination with expert opinion, including a Delphi exercise, and a consensus meeting of the ASessments in AS (ASAS) Working Group.

**Results:** The final consensus comprises the following requirements: (1) For the *initiation* of anti-TNF $\alpha$  therapy: (a) a diagnosis of definitive AS; (b) presence of active disease for at least four weeks as defined by both a sustained Bath AS Disease Activity Index (BASDAI) of at least 4 and an expert opinion based on clinical features, acute phase reactants, and imaging modalities; (c) presence of refractory disease defined by failure of at least two non-steroidal anti-inflammatory drugs during a single three month period, failure of intra-articular steroids if indicated, and failure of sulfasalazine in patients with peripheral arthritis; (d) application and implementation of the usual precautions and contraindications for biological therapy. (2) For the *monitoring* of anti-TNF $\alpha$  therapy: both the BASDAI and the ASAS core set for clinical practice should be followed regularly. (3) For the *discontinuation* of anti-TNF $\alpha$  therapy: in non-responders, consideration should be made after 6–12 weeks' treatment. Response is defined as improvement of (a) at least 50% or 2 units (on a 0–10 scale) of the BASDAI, (b) expert opinion that treatment should be continued.

**Conclusion:** This consensus statement on anti-TNF $\alpha$  treatment in AS may be used for guidance in clinical decision making and as the basis for the development of guidelines. Evaluation of the healthcare consequences of this consensus is subject to further research by the ASAS group.

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Accepted 27 May 2003

Ankylosing spondylitis (AS) is a chronic inflammatory disease that generally begins early, often in the third decade of life. The prevalence is at least 0.1%, but has been reported to be a lot higher.<sup>1,2</sup> Women are not as commonly affected as men, but the overall disease impact may be similar. At least one third of patients with AS carry a heavy burden of disease that leads to severe disability.<sup>3</sup> The long term consequences of AS are similar to those seen in rheumatoid arthritis (RA), with associated high direct and indirect costs for society.<sup>4–6</sup> For patients with AS, overall health related quality of life is decreased,<sup>7</sup> and mortality is increased.<sup>8</sup>

Internationally accepted criteria have been developed and evaluated to classify and diagnose AS<sup>9</sup> and other spondyloarthritides (SpA).<sup>10</sup> Four other SpA subgroups can be differentiated: psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease, and undifferentiated SpA. Patients diagnosed with an SpA other than AS may still develop AS during their disease course. The recommendations in this consensus statement will be limited to patients with definitive AS.

Instruments and criteria sets have been developed and validated to assess disease activity<sup>11</sup> and functional status<sup>12</sup> of patients with AS. Furthermore, a proposal for staging of patients with AS has been made recently,<sup>13</sup> and core sets of outcome parameters have been agreed upon by an international expert group, the ASessments in AS (ASAS) Working Group,<sup>14,15</sup> which has recently also developed improvement criteria for AS.<sup>16</sup>

Over the past few decades, treatment for AS has consisted mainly of non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. In contrast with RA, disease modifying

antirheumatic drugs (DMARDs) work only to a limited extent in peripheral arthritis but not in axial disease (reviewed by Leirisalo-Repo<sup>17</sup> and Braun and Sieper<sup>18</sup>).

There is now increasing evidence that anti-tumour necrosis factor (anti-TNF $\alpha$ ) therapy is efficacious not only for RA but also in patients with AS and other forms of SpA. Three anti-TNF $\alpha$  agents are currently approved for the treatment of RA in the USA and Europe: infliximab (in RA, in combination with methotrexate), etanercept, and adalimumab. Infliximab is also approved for Crohn's disease, while etanercept is approved for psoriatic arthritis and juvenile chronic arthritis.

In AS, there has been consistent benefit with the use of anti-TNF $\alpha$  therapy, shown initially in pilot studies,<sup>1,20</sup> open,<sup>21–24</sup> follow up studies,<sup>25–27</sup> and, most importantly, in several randomised controlled trials.<sup>28–32</sup> Anti-TNF $\alpha$  therapy may provide substantial benefit for patients, and imaging techniques (magnetic resonance imaging (MRI) and ultrasound) provide additional objective evidence for improvement of inflammation in affected structures such as peripheral entheses and spinal structures.<sup>33–35</sup> As of May 2003, infliximab has been approved for the treatment of patients with AS in

**Abbreviations:** AS, ankylosing spondylitis; ASAS, ASessments in AS; BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; CRP, C reactive protein; DC-ART, disease controlling antirheumatic treatment; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SpA, spondyloarthritides; TNF $\alpha$ , tumour necrosis factor  $\alpha$ ; VAS, visual analogue scale

Europe and Mexico. It seems likely that infliximab and etanercept will be both approved during 2003 in Europe and possibly also in the USA.

Guidelines are currently needed to ensure appropriate selection of patients suitable for anti-TNF $\alpha$  therapy, which can lead to harm, with rare, but possible, side effects, such as serious infections and demyelinating disease (reviewed by Antoni and Braun<sup>36</sup>). However, it is largely accepted that the risk/benefit ratio of this treatment is favourable and advantageous for most patients. Nevertheless, although beneficial for most patients, anti-TNF $\alpha$  therapy does not seem to be efficacious in all patients. In RA, guidelines on the use of TNF $\alpha$  blocker therapy have been developed.<sup>37, 38</sup>

As a consequence of limited budget resources and the relatively high costs of anti-TNF $\alpha$  therapy, patients with the best risk/benefit ratio should be treated. There is need to identify patients with AS with active disease who are at increased risk of severe disease, with deterioration of functional capacities, and who therefore are the best candidates, as they have the most to gain from the use of anti-TNF $\alpha$  treatment. Although evidence is preferred to expert opinion, a scarcity of data which can answer these questions necessitates a consensus statement from the leading experts in the field, to give guidance for initiation, monitoring, and discontinuation of anti-TNF $\alpha$  therapy.

Recommendations for anti-TNF $\alpha$  therapy in AS are provided for patients, general physicians, rheumatologists, healthcare providers, payers, and governmental agencies. The primary aim of this ASAS initiative, however, was to produce guidelines for rheumatologists and other experts in the management of AS, as well as to guide payers into this new important era of targeted treatment. Whereas these recommendations are most relevant for daily clinical practice in rheumatology, we hope that they will be more widely adopted by other doctors to ensure that patients with very active and severe disease are referred to experts who can provide the appropriate treatment.

## METHODS

This manuscript has been developed on the basis of:

1. Contributions of all participating ASAS members
2. Discussions among the members of the ASAS steering committee who developed the questionnaires and facilitated the committee dialogues
3. Results of several questionnaires, including a formal Delphi exercise
4. Trial data and observational databases analysed
5. Discussions during the consensus meeting in Berlin.

The first step was a Delphi exercise among the ASAS members that is published in detail in this issue of the journal (see p 812).<sup>39</sup> In preparation for the consensus meeting, two additional questionnaires were sent to all ASAS members to facilitate discussion. The content and the results of these questionnaires are not given in detail in this paper. Data derived from the questionnaires are only presented if the results were influential in the subsequent decision making required in the consensus statements.

The systematic order of this manuscript, as implemented in the development of guidelines proposed by the British National Institute for Clinical Excellence (NICE) publication was very influential in our deliberations.<sup>38</sup>

In line with the AGREE instrument,<sup>40</sup> this paper intends to define the scope, purpose, and potential health impact of the consensus statement.

The requirements of this instrument include that

- The clinical question is clearly described and the target population is identified

- Relevant stakeholders are involved in the development of this consensus statement. However, among the professional groups, only one patient with AS (MA Khan) and no doctors of other specialties have thus far participated in this consensus report
- A definition of target users is given and the recommendations are piloted among users
- The development of these guidelines is rigorous, using systematic methods and accepted criteria for selecting evidence
- These recommendations are formulated to facilitate both doctor and patient understanding and that the risks and benefits of initiating TNF $\alpha$  blocker therapy are discussed
- The link between our recommendations and the supporting evidence is clearly described. The recommendations were externally reviewed by two senior ASAS members who were not present at the meeting (AC and JE) and internally by all authors who are all members of the steering committee and MAK.
- The guidelines will be updated regularly. This is planned to take place in a similar meeting in about two years
- The different options for management of AS are discussed in detail. This has not been done exhaustively in this manuscript, because it has been extensively reviewed in recent papers<sup>18</sup>
- The cut off points selected are easily identified and the tools are selected on the basis of a core set published by this group
- The guidelines are easily applicable and there are no organisational barriers.
- Cost implications are considered. While mindful of costs in this process, costs were only partly considered in this manuscript
- Key review criteria for monitoring are included
- Given that the authors are independent, no conflict of interest needs to be disclosed.

The manuscript of the Spondyloarthritis Research Consortium of Canada<sup>41</sup> on anti-TNF $\alpha$  therapy was made available to all participants before the meeting.

The ASAS working group meeting took place on the 24 and 25 January 2003 in Berlin, Germany. The meeting was financially supported by five pharmaceutical companies (see "Acknowledgements"), and was organised under the auspices of the ASAS steering committee. The sponsoring pharmaceutical companies had no formal voting during the consensus, and had no influence on the development of the consensus statements or this manuscript. All ASAS members are member of the working group. One can become a member by an application to the advisory board of a person showing a dedicated interest in AS research visible in publications. The steering committee comprises six members and leads the group. The advisory board consists of all steering committee members and several advisors to help guide the direction of the group.

## RESULTS

### General recommendations

Infliximab and etanercept are both recommended for the treatment of patients with active AS whose disease cannot be satisfactory managed conventionally.

Use of these agents and the follow up of response should be undertaken only by an experienced rheumatologist, or other locally recognised expert, who can provide specialised advice on their use. The choice of anti-TNF $\alpha$  should be determined by consultation between the patient and doctor, taking into account differences in treatment schedules and patient

preferences. Maintenance treatment with these agents should be at the lowest recommended dose compatible with continuing clinical response.

It is recommended that all clinicians prescribing these agents should preferably register patients in a national register, which may need to be established in some countries, to collect information on outcome and toxicity of anti-TNF $\alpha$  agents.

The current long term experience with TNF $\alpha$  blocker therapy in AS is now about two years. More data on long term treatment beyond two years are currently being collected. There is no evidence that the long term use of these agents must be discouraged, there is just a need for more data. Evidence for the consecutive use of different agents is limited. Therefore, successive use of different TNF $\alpha$  blocker drugs cannot be recommended at the present time. As further data become available, these will be used to guide decision making.

### Clinical need and practice

- AS is a chronic, progressive, destructive, and disabling condition that carries significant morbidity and mortality rates. The disease has a severe impact on patient quality of life and represents a considerable economic burden.
- AS is characterised by inflammation in the axial skeleton, sacroiliac joints, peripheral joints, and entheses, which causes pain, stiffness, and swelling, potentially leading to destruction and/or ankylosis of the structures affected. About 30% of patients with AS have severe disease often accompanied by considerable functional loss.<sup>3</sup>
- AS is the most common inflammatory spinal disease in the world, affecting a rather high percentage of the population. Owing to the strong association of AS with HLA-B27, there is a gradual decline in the prevalence of AS from populations indigenous to the Northern latitude to those that are indigenous to more Southern latitudes. On the basis of very conservative estimates, there may be considerably more than 600 000 patients with AS in Europe and 350 000 in the USA.<sup>42</sup> Rates may be 10 times higher than this, however, and high quality epidemiological data are lacking for many areas of the world.
- Management of AS requires a multidisciplinary approach, with physical therapy and sometimes also surgical interventions running in parallel with drug treatment. Key aims of treatment include control of pain and stiffness, as well as reducing damage, disability, and loss of function.
- Conventional treatment consists mainly of drug treatment with NSAIDs, corticosteroid injections, and sulfasalazine in patients with peripheral arthritis. Methotrexate is also recognised to be widely used, but there is no evidence of benefit.
- Patients with active AS who have an inadequate response to NSAIDs are possible candidates for anti-TNF $\alpha$  therapy. The situation concerning treatment with DMARDs in AS differs from that in RA.

### The technologies

TNF $\alpha$  is a proinflammatory mediator that has been identified as an important molecule in the pathogenesis of AS and related SpA. Messenger RNA of TNF $\alpha$  has been detected in biopsy specimens taken from sacroiliac joints of patients with AS.<sup>43</sup>

#### Infliximab

Infliximab is a monoclonal chimeric human anti-TNF $\alpha$  antibody that binds with high affinity to TNF $\alpha$ . It is currently licensed for the treatment of RA to reduce signs and symptoms of RA in patients with active disease, to improve the physical function of patients, and to reduce the rate of

progression of joint damage. Infliximab is approved for combination therapy with methotrexate in RA in a dose of 3 mg/kg given every eight weeks after the usual initial saturation phase, where infliximab is given at weeks 0, 2, and 6. Furthermore, infliximab is approved for acute and maintenance treatment of Crohn's disease in a dose of 5 mg/kg. Infliximab is given as an intravenous infusion usually over 1–2 hours.

#### Etanercept

Etanercept is a recombinant 75 kDa TNF $\alpha$  p75 receptor fusion protein that acts competitively to inhibit the cell surface receptor binding of TNF $\alpha$ . It is licensed for the treatment of active RA when the response to DMARDs, including methotrexate, has been inadequate. Etanercept is administered by subcutaneous injection at a dose of 25 mg twice weekly.

#### Adalimumab

Adalimumab is a monoclonal, fully human, anti-TNF $\alpha$  antibody that binds with high affinity to TNF $\alpha$ . It is approved for the treatment of active RA in the USA. It is given by subcutaneous injection at a dose of 40 mg every two weeks or weekly.

### Clinical effectiveness in AS

Data on clinical effectiveness in AS have recently been extensively reviewed<sup>18</sup> and evaluated by Canadian rheumatologists.<sup>41</sup> The important studies providing the evidence are listed below:

- Infliximab<sup>19–24 26–30 34–36</sup>
- Etanercept<sup>25 31–33</sup>
- Adalimumab (no available studies, one randomised controlled trial planned).

Taken together there is no reasonable doubt that anti-TNF $\alpha$  therapy is very efficacious in AS, and the efficacy is probably even stronger than in RA.

### Cost effectiveness

Randomised controlled trials have provided substantial evidence that the quality of life of patients with AS who are treated is increased to a relevant extent. Costs for quality of life years have not been calculated to date.

No studies have dealt with the question of costs prospectively. However, from the socioeconomic data already available<sup>4–6</sup> it seems possible that anti-TNF $\alpha$  therapy is cost effective in patients with AS, and appropriate analyses are underway to answer this question (Boonen A, Maetzel A, Kobelt G, manuscripts in preparation).

### Considerations

1. Results of the available clinical trials provide strong evidence of the clinical effectiveness of infliximab and etanercept, and are supported by continuation data of up to one year. Currently there is no other known disease controlling antirheumatic treatment for AS. This is in sharp contrast with RA, where many DMARDs are known to be effective.

2. The optimal dosages of both agents are somewhat uncertain because no dose finding or direct comparative studies have been performed. For infliximab, doses of 3 mg/kg and 5 mg/kg and treatment intervals of between six and 14 weeks have been used. At present, most data are available for a dose of 5 mg/kg every six weeks. However, lower doses and longer intervals may also work in subgroups of patients and the issue of adding an immunosuppressant drug, such as methotrexate or azathioprine, to increase the effects of infliximab and possibly also of other TNF $\alpha$  blockers is unresolved.<sup>44</sup>

3. No clear advantage of the efficacy of one agent over the other has been identified, but etanercept has been shown to

lack efficacy in patients with concomitant gut involvement such as Crohn's disease.<sup>45</sup> In contrast, etanercept is effective in patients with psoriatic arthritis.<sup>46, 47</sup>

4. The term disease controlling antirheumatic treatment (DC-ART) has been proposed by the WHO to differentiate this type of drug from symptom modifying antirheumatic drugs such as NSAIDs. The term DMARDs is also currently used to identify DC-ART drugs. In this manuscript, the terms DC-ART or DMARD are not used for the anti-TNF $\alpha$  agents. Anti-TNF $\alpha$  agents have been proved to be symptom modifying and it seems likely that they have also disease modifying and disease controlling abilities. However, there is no international consensus to date on whether the biological agents should be categorised as DMARDs or DC-ART. Thus, it is better to group them separately at present.

### Implications

If the most conservative estimate of the prevalence and severity of AS is used, several hundred thousand European patients with AS are potential candidates for this treatment. The patients with contraindications to this treatment (in RA 15%), the patients who do not respond to this treatment, and the patients who withdraw for other reasons (in AS about 20% in the first year) have to be subtracted. Furthermore, the possibility of longlasting benefit after discontinuation needs to be considered. Substantial costs of other treatments and indirect costs related to decreased function and disability now consumed by these patients may become unnecessary and could be saved.

The differences in the delivery of infliximab and etanercept also need to be mentioned because infliximab is infused whereas etanercept may be self injected. Thus, a greater demand for day case facilities can be expected. The patients seem to have no clear cut favourite mode of drug delivery in general.

Because the drug costs are still quite high, this burden of costs needs to be considered in individual national health systems.

### Further research

The long term impact of anti-TNF $\alpha$  therapy in AS is unclear at present. Further study is needed to examine the effects of anti-TNF $\alpha$  therapy on radiological progression. A reduced risk of joint damage and disability may reduce the incidence of hip joint replacements and other types of surgery. The possibility of discontinuation of treatment after longlasting benefit needs to be studied. Addition of immunosuppressant drugs may decrease the need for high doses and short intervals of treatment with infliximab.<sup>44</sup>

The use of biological registries is highly recommended to answer some of these important clinical and economic questions.

### Implementation

Clinicians treating patients with AS should review and contrast their current practices against the recommendations provided in this manuscript. Each patient should be carefully documented to aid in the development of future registries.

These recommendations are published in the *Annals of the Rheumatic Diseases*, the official journal of EULAR, and they are available on the website of the *Annals of the Rheumatic Diseases* and on the ASAS website.

## CONSENSUS GUIDANCE FOR TREATMENT OF AS WITH ANTI-TNF $\alpha$

The following structure for the recommendation was agreed upon (see also table 1):

- Diagnosis
- Failure of standard treatment

- Disease activity
- Exclusion criteria
- Monitoring and withdrawal.

### Diagnosis

In accordance with the results of the Delphi exercise, there was agreement that patients would be identified as having AS if they met the criteria of the modified New York criteria.<sup>9</sup> However, it was recognised that there is a wider range of SpA, especially undifferentiated SpA, which are not covered by these criteria. The group also identified weaknesses of the modified New York criteria both in assessing sacroiliitis reliably on radiographs and in overlooking early cases based on the radiographic criterion. Although other criteria were considered, such as the ESSG or Amor criteria, the conference participants decided that the modified New York criteria were preferred because all studies used these as inclusion criteria. There was also agreement that more data are needed on anti-TNF $\alpha$  therapy in patients with undifferentiated SpA. In the future, it is conceivable that patients who do not fulfil the radiographic part of the modified New York criteria but show evidence of active disease, such as evidence of sacroiliitis or spinal inflammation by MRI, would be suitable candidates for anti-TNF $\alpha$  therapies.

It was further discussed whether separation of disease manifestations according to differing clinical presentations—such as axial disease, peripheral arthritis, and enthesitis—was useful. For the initial assessment of disease activity, the decision was made to examine the overall clinical picture. However, it was also clear that, for the definition of both active disease and treatment failure, differentiation into the three main disease manifestations—axial disease, peripheral arthritis, and enthesitis—should be considered.

Furthermore, there was agreement that the assessment of disease activity should be generally derived from two different sources, one being entirely patient reported and the other based on an expert's opinion taking into account all available information. The exact definition that was selected will be presented under disease activity.

There was agreement that no definition of minimal or maximal disease duration should be required to be met to use anti-TNF $\alpha$  therapy. The modified New York criteria imply that the duration of inflammatory back pain has exceeded three months. Moreover, it is obvious from published reports that there is a long delay between symptom onset and establishing a diagnosis, especially because documented evidence of radiographic sacroiliitis is required.

### Failure of standard treatment

For all three disease presentations manifested as axial disease, peripheral arthritis, and enthesitis, treatment failure was defined as a trial of at least three months of standard NSAID treatment. Before starting anti-TNF $\alpha$  therapy, patients must have had an adequate therapeutic trial of at least two NSAIDs. Doctors should use maximal recommended or tolerated anti-inflammatory doses, unless these drugs are contraindicated.

The failure of NSAID treatment is required for all three presentations—axial disease, peripheral arthritis, and enthesitis:

- For symptomatic axial disease, no additional treatment is required before initiation of anti-TNF $\alpha$  therapy
- For symptomatic peripheral arthritis, failure of intra-articular corticosteroid treatment (at least two injections) is normally required in oligoarthritis. Unless contraindicated or not tolerated, standard DMARD treatment with sulfasalazine at maximally tolerated doses up to 3 g/day should be prescribed for four months
- For symptomatic enthesitis, an adequate therapeutic trial of at least two local steroid injections is normally required, as long as these injections are not contraindicated.

### Disease activity

There was agreement that, in general, three aspects should be considered which may possibly indicate the need for biological treatment:

- Persistence of active disease
- Threat of severe disease (damage)
- Likelihood of response to treatment.

The first category represents a clear cut therapeutic approach, the second has a more preventive character, and the third intends to preselect patients with potentially good responses to treatment. Markers of disease, such as C reactive protein (CRP) and rapid radiographic progression, were regarded as useful for determining the threat of severe disease and the likelihood of response to treatment. However, in the absence of data it was decided to concentrate on disease activity. As more data become available, information about the failure of standard treatment and disease activity will require updating at future meetings.

After an intensive discussion it was decided that, for the assessment of disease activity, both the Bath AS Disease Activity Index (BASDAI) and an expert opinion are required. The following definitions were given to define expert opinion: (a) the expert should be a doctor, usually a rheumatologist, with expertise in inflammatory back pain and the use of anti-TNF $\alpha$  blocking agents, and (b) expert opinion should include clinical features, acute phase reactants, and imaging modalities. Valid imaging methods include radiographs demonstrating rapid progression and MRI scans indicating inflammation.

There was consensus that the BASDAI represents the patient perspective of disease activity given that it was developed in close collaboration with patients and has a high correlation with other measures, including patient global assessment.

The experts were in agreement that function is a very important outcome measure in AS that can be easily assessed by the Bath AS Functional Index (BASFI). Function in AS correlates with both disease activity and damage. Disease activity is evaluated by the BASDAI; given that the goal of evaluation is not to identify predictors of severe disease, assessment of structural damage has a lower priority. There was consensus that the second assessment of disease activity should be made by an expert with extensive knowledge of the disease and experience with TNF $\alpha$  blocker therapy. It was also emphasised that disease activity should be strictly related to AS associated inflammatory disease (and not to mechanical back pain, for example). Overall, the role of the expert is to decide whether a patient is an appropriate candidate given the possible harms and benefits of anti-TNF $\alpha$  therapy. The identification of an expert should be made locally, and should take into consideration the usual referral patterns in that area, that country, and preferably should involve recognition by a national society. To make an informed decision, the expert should have available clinical features (history and examination), as well as either serum acute phase reactant levels or imaging results.

Appropriate imaging modalities to assess the presence of disease might include some or all of sacroiliac joint and spinal x ray examination, computed tomography, and MRI. Assessment of disease activity by imaging is mainly possible with MRI.<sup>48</sup> However, it was recognised that MRI is not widely available, not yet standardised, and is still quite costly. Rapid radiographic progression over 1–2 years was also considered to be an indicator of high disease activity. Other modalities were considered, including scintigraphy and ultrasound, but no recommendations were made on their use for this document. However, it was also recognised that experience at various medical centres might differ and studies on these issues are continuing.

When BASDAI scores are used, a cut off point for moderate to severe disease needs to be defined. There was agreement

that a BASDAI score  $\geq 4$  on either a visual analogue scale (VAS) or a numerical rating scale (NRS) with a range of 0–10 should be required. However, on the basis of a small French dataset,<sup>23</sup> a BASDAI cut off point of 3 may also lead to clinically relevant improvement of patients with AS.

The likely response to treatment was discussed and it was concluded that most patients will benefit from anti-TNF $\alpha$  therapy. Furthermore, it was recognised that there are no good predictors for treatment response. Most data are based on studies using BASDAI scores greater than or equal to 4 for inclusion; furthermore, most data have been obtained with CRP positive patients.

It was recommended that the BASDAI should be  $\geq 4$  and that expert opinion should be recorded at two different times about one month apart. However, it was recognised that in a patient with very active disease, an earlier start of treatment might be desirable. Thus one should keep in mind the requirement for a three month trial of NSAID treatment. If a patient is referred to an expert for initiation of TNF $\alpha$  blocking therapy, the assessment made by the first doctor may count as the first observation.

### Exclusion criteria

There was agreement that there are no AS-specific exclusion criteria; however, there may be specific exclusion criteria for an individual drug regimen. Such exclusions should be obtained from the drug manufacturer or other sources such as recommendations of societies.

Importantly, the doctor should obtain any history of current or recurrent infections, pregnancy/lactation, tuberculosis, multiple sclerosis, lupus, or malignancy.

There are, or will be, recommendations on how to prevent tuberculosis in each country. Such guidelines should be followed.

Currently, no evidence excludes patients with complete spinal fusion. However, these patients may have a less dramatic response to treatment given that some of their complaints stem from mechanical restriction and disability rather than from inflammatory disease.

### Monitoring and withdrawal

#### Monitoring

The following list for monitoring patients receiving biological agents was discussed:

- Patient global assessment
- Pain
- Spinal mobility including chest expansion, modified Schober test, lateral spinal flexion, and occiput to wall distance measurements
- BASDAI
- BASFI
- Number of swollen joints
- Erythrocyte sedimentation rate (ESR)/CRP

Table 1 lists the ASAS core set for clinical practice.

The ASAS core set of outcome parameters for clinical practice<sup>15</sup> has already been defined. The use of this core set is recommended for following up patients in clinical practice. In addition, the BASDAI should be applied to assess the response to treatment.

#### Withdrawal

There was agreement that an assessment of response, and consideration of whether treatment with biological agents should be discontinued, should be undertaken after 6–12 weeks. No definition of intervals between assessments was considered necessary.

Minimal clinically important improvement is defined as a reduction by 2 in the BASDAI score, and thus it was decided to

**Table 1** ASAS consensus for anti-TNF therapy

	Specification (definition of the terms)
<b>Patient selection</b>	
• Diagnosis	<ul style="list-style-type: none"> <li>• Patients normally fulfilling modified New York Criteria for definitive AS</li> <li>• <b>Modified New York criteria 1984</b> (van der Linden <i>et al</i>)<sup>*</sup> <ul style="list-style-type: none"> <li>• <b>Radiological criterion</b> <ul style="list-style-type: none"> <li>• Sacroiliitis, grade <math>\geq</math>II bilaterally or grade III to IV unilaterally</li> </ul> </li> <li>• <b>Clinical criteria</b> (2 out of the following 3) <ul style="list-style-type: none"> <li>• Low back pain and stiffness for &gt;3 months that improves with exercise but is not relieved by rest</li> <li>• Limitation of motion of the lumbar spine in both the sagittal and frontal planes</li> <li>• Limitation of chest expansion relative to normal values correlated for age and sex</li> </ul> </li> </ul> </li> </ul>
• Active disease	<ul style="list-style-type: none"> <li>• Active disease for <math>\geq</math>4 weeks</li> <li>• BASDAI <math>\geq</math>4 (0–10) and an expert* opinion that anti-TNF treatment should be started<sup>†</sup></li> </ul>
• Treatment failure	<ul style="list-style-type: none"> <li>• All patients must have had adequate therapeutic trials of at least 2 NSAIDs. An adequate therapeutic trial is defined as: <ul style="list-style-type: none"> <li>• Treatment for <math>\geq</math>3 months at maximal recommended or tolerated anti-inflammatory dose unless contraindicated</li> <li>• Treatment for &lt;3 months where treatment was withdrawn because of intolerance, toxicity, or contraindications</li> </ul> </li> <li>• Patients with symptomatic peripheral arthritis (normally having a lack of response to a local steroid injection for those with oligoarticular involvement) must have had adequate therapeutic trial of both NSAIDs and sulfasalazine<sup>‡</sup></li> <li>• Patients with symptomatic enthesitis must have had an adequate therapeutic trial of at least two local steroid injections unless contraindicated</li> </ul>
• Contraindication	<ul style="list-style-type: none"> <li>• Women who are pregnant or breastfeeding; effective contraception must be practised</li> <li>• Active infection</li> <li>• Patients at high risk of infection including: <ul style="list-style-type: none"> <li>• Chronic leg ulcer</li> <li>• Previous tuberculosis (note: please follow local recommendations for prevention or treatment)</li> <li>• Septic arthritis of a native joint within the past 12 months</li> <li>• Sepsis of a prosthetic joint within the past 12 months, or indefinitely if the prosthesis remains in situ</li> <li>• Persistent or recurrent chest infections</li> <li>• Indwelling urinary catheter</li> </ul> </li> <li>• History of lupus or multiple sclerosis</li> <li>• Malignancy or premalignancy states excluding: <ul style="list-style-type: none"> <li>• Basal cell carcinoma</li> <li>• Malignancies diagnosed and treated more than 10 years previously (where the probability of total cure is very high)</li> </ul> </li> </ul>
<b>Assessment of disease</b>	
• ASAS core set for daily practice	<ul style="list-style-type: none"> <li>• Physical function (BASFI or Dougados functional index)</li> <li>• Pain (VAS, past week, spine at night, due to AS and VAS, past week, spine due to AS)</li> <li>• Spinal mobility (chest expansion and modified Schober test and occiput to wall distance and lateral lumbar flexion)</li> <li>• Patient's global assessment (VAS, past week)</li> <li>• Stiffness (duration of morning stiffness, spine, past week)</li> <li>• Peripheral joints and entheses (number of swollen joints (44 joint count), enthesitis score such as developed in Maastricht, Berlin, or San Francisco)</li> <li>• Acute phase reactants (ESR or CRP)</li> <li>• Fatigue (VAS)</li> </ul>
• BASDAI	<ul style="list-style-type: none"> <li>• VAS overall level of fatigue/tiredness past week</li> <li>• VAS overall level of AS neck, back, or hip pain past week</li> <li>• VAS overall level of pain/swelling in joints other than neck, back or hips past week</li> <li>• VAS overall discomfort from any areas tender to touch or pressure past week</li> <li>• VAS overall level of morning stiffness from time of awakening past week</li> <li>• Duration and intensity (VAS) of morning stiffness from time of awakening (up to 120 minutes)</li> </ul>
<b>Assessment of response</b>	
• Responder criteria	BASDAI: 50% relative change or absolute change of 2 (scale 0–10) and expert opinion: Continuation yes/no
• Time of evaluation	Between 6 and 12 weeks

VAS, visual analogue scale; all VAS can be replaced by a numerical rating scale (NRS).

\*The expert is a doctor, usually a rheumatologist, with expertise in inflammatory back pain and the use of biological agents. Experts should be locally defined; <sup>†</sup>an expert opinion comprises clinical features (history and examination), serum acute phase reactant levels, or imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating inflammation; <sup>‡</sup>sulfasalazine: treatment for  $\geq$ 4 months at standard target dose of 3 g/day, or maximally tolerated dose unless contraindicated or not tolerated. Treatment for <4 months, where treatment was withdrawn because of intolerance or toxicity or contraindicated.

suggest the following: discontinuation of biological treatment should be considered in patients who do not have either a 50% relative or a two point absolute improvement in the BASDAI score assessed on an NRS (equivalent to 20 mm on a VAS).

## CONCLUSIONS

This is the first international consensus statement on the initiation, monitoring, and withdrawal of anti-TNF $\alpha$  therapy in AS. Anti-TNF $\alpha$  therapy is likely to change completely the therapeutic approach to these patients, especially those with refractory, severe, and active disease.

It is hoped that this consensus will be widely accepted and implemented. The consensus is the product of a multinational committee who have a dedicated interest in treating patients with AS. Furthermore, it is the result of a transparent process within the ASAS group. Before the meeting in Berlin, most ASAS members underwent a long preparation process involving the use of both the Delphi exercise and additional questionnaires.

The challenge was to provide an answer to the three major issues about anti-TNF $\alpha$  therapy of patients with AS:

1. Which patients are appropriate for treatment?

## 2. How to monitor response to treatment?

## 3. When to discontinue treatment?

This document is more comprehensive than those which have been produced for RA, where the focus has been mainly on the initiation of treatment.

This consensus statement is somewhat different from the Canadian statement which was produced slightly earlier. However, the main recommendations of the two proposals are consistent.

In the opinion of the ASAS members, the present document could best be described as a consensus statement. After external review and further testing, the recommendations in this document could be considered to be official guidelines. An evaluation and update will be published after two years.

## ACKNOWLEDGEMENTS

We acknowledge the contributions of the ASAS members, who either participated in the meeting or completed the questionnaires, or both (appendix 1).

The consensus meeting in Berlin was financially supported by unrestricted grants from Abbott, Amgen, Centocor, Schering Plough, and Wyeth. There are no other financial disclosures. The sponsors had no role in voting, or in developing the final document.

## Appendix 1: List of participants/questionnaire coworkers

Adebajo AO, UK; Amor B, France; Boers M, The Netherlands; Boonen A, The Netherlands; van den Bosch FEJ, Belgium; Brandt J, Germany; Braun J, Germany\*; Burgos Vargas R, Mexico; Calin A, UK; Clegg D, USA; Collantes Estevez E, Spain; Darmawan J, Indonesia; Davis J, USA\*; Dougados M, France\*; Dijkmans BAC, The Netherlands; Edmonds J, Australia; Emery P, UK; Feltelius N, Sweden; Géher P, Hungary; Guillemin F, France; van der Heijde DMFM, The Netherlands\*; Horst v.d.-Bruinsma I, The Netherlands; Khan MA, USA; Kirazli J, Turkey; Kuipers JG, Germany; Landewé R, The Netherlands; Leirisalo-Repo M, Finland; van der Linden SJ, The Netherlands\*; Linszen A, The Netherlands; Listing J, Germany; Maetzel A, Canada; Maksymowych W, Canada; Mielants H, Belgium; Olivieri I, Italy; Peloso P, USA; Pham T, France; Reveille J, USA; P van Riel, The Netherlands; Rudwaleit M, Germany; Russell AS, Canada; Salvarani C, Italy; Sieper J, Germany\*; Stone MA, Canada; Sturrock R, UK; Yu D, USA; Zeidler H, Germany.

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