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

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Objective: To obtain an international consensus about the use of anti-tumour necrosis factor α (anti-TNFα) 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 ASsessments in AS (ASAS) Working Group.

Results: The final consensus comprises the following requirements: (1) For the initiation of anti-TNFα therapy: (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-TNFα therapy: both the BASDAI and the ASAS core set for clinical practice should be followed regularly. (3) For the discontinuation of anti-TNFα therapy: 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-TNFα 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.
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-TNFα therapy, which can lead to harm, with rare, but possible, side effects, such as serious infections and demyelinating disease (reviewed by Antoni and Braun"). 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-TNFα therapy does not seem to be efficacious in all patients. In RA, guidelines on the use of TNFα blocker therapy have been developed.17 18

As a consequence of limited budget resources and the relatively high costs of anti-TNFα 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-TNFα therapy. 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-TNFα therapy.

Recommendations for anti-TNFα 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).19 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.14 In line with the AGREE instrument,18 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 TNFα 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 papers19

• 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 Canada20 on anti-TNFα 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 satisfactorily 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 advise on their use. The choice of anti-TNFα 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-TNFα agents.

The current long term experience with TNFα 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 TNFα 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.
• 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. 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-TNFα therapy. The situation concerning treatment with DMARDs in AS differs from that in RA.

The technologies

TNFα is a proinflammatory mediator that has been identified as an important molecule in the pathogenesis of AS and related SpA. Messenger RNA of TNFα has been detected in biopsy specimens taken from sacroiliac joints of patients with AS.

Infliximab
Infliximab is a monoclonal chimeric human anti-TNFα antibody that binds with high affinity to TNFα. 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 TNFα p75 receptor fusion protein that acts competitively to inhibit the cell surface receptor binding of TNFα. 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-TNFα antibody that binds with high affinity to TNFα. 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 reviewed49 and evaluated by Canadian rheumatologists.50 The important studies providing the evidence are listed below:

• Infliximab24 26–30 34–36
• Etanercept25 11–13
• Adalimumab (no available studies, one randomised controlled trial planned).

Taken together there is no reasonable doubt that anti-TNFα 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 available51 it seems possible that anti-TNFα 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 3 mg/kg every six weeks. However, lower doses and longer intervals may also work in subgroups of patients and the intended use of adding an immunosuppressant drug, such as methotrexate or azathioprine, to increase the effects of infliximab and possibly also of other TNFα blockers is unresolved.49

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. In contrast, etanercept is effective in patients with psoriatic arthritis. In contrast, etanercept is effective in patients with psoriatic arthritis.

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-TNFα agents. Anti-TNFα 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-TNFα therapy in AS is unclear at present. Further study is needed to examine the effects of anti-TNFα 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. 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-TNFα**
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. 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-TNFα 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-TNFα 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-TNFα 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-TNFα 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-TNFα 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)

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. 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, 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\(^3\) 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
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-TNFα therapy in AS. Anti-TNFα 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-TNFα 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 exter-
nal 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
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References

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Ann Rheum Dis 2003 62: 817-824
doi: 10.1136/ard.62.9.817

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