First Update of the International ASAS Consensus Statement for the Use of Anti-TNF Agents in Patients with Ankylosing Spondylitis

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Key words: therapy, ankylosing spondylitis, tumor necrosis factor (TNF)-α, infliximab, etanercept, adalimumab, consensus, recommendations

Word Count: 2655

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Abstract

**Background.** In the first consensus statement on anti-TNFα therapy in patients with ankylosing spondylitis (AS) published in 2003 the ASsessment in AS (ASAS) international working group decided to update the recommendations every 2 years. This is the first biyearly update for the initiation, monitoring, and discontinuation of such agents in AS.

**Objective.** To update the international consensus and recommendations for the use of anti-TNF agents in the clinical practice of treating patients with AS.

**Methods.** The published recommendations on anti-TNF therapy in AS patients formed the basis of this update. The update was facilitated by a questionnaire sent to the ASAS members before the final decisions were agreed upon at an international meeting of the ASAS working group.

**Results.** Overall, the participants were satisfied with the published recommendations. Consequently, only minor changes to the original consensus statement were required: 1.] For the initiation of anti-TNF therapy: a.) a diagnosis of definitive AS (normally based on modified New York criteria); b.) active disease for at least 4 weeks as defined by both a sustained Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of > 4 on a 0-10 scale and an expert opinion based on clinical features, acute phase reactants, and imaging modalities; c.) refractory disease defined by failure of at least 2 nonsteroidal anti-inflammatory drugs (NSAIDs) during a 3 month period, failure of intraarticular steroids (if indicated), and failure of sulfasalazine in patients with predominantly peripheral arthritis; d.) application of the usual precautions and contraindications for biologic therapy should be followed. 2.] For the monitoring of anti-TNF therapy: both the ASAS core set for clinical practice and the BASDAI should be followed after the initiation of treatment. 3.] The discontinuation of anti-TNF therapy in non-responders should be considered after 6-12 weeks of therapy. Response is defined by improvement of a.) at least 50% or 2 units (on a 0-10 scale) of the BASDAI and b.) expert opinion that treatment should be continued.

**Conclusion.** This updated consensus statement is recommended in guiding clinical practice and may serve as a basis for development of national guidelines. Evaluation and regular update of this consensus statement is subject to further research by the ASAS group.
Introduction

Anti-TNF therapy is considered a major advance in the treatment of patients with ankylosing spondylitis (AS). Recommendations for anti-TNF therapy in patients with AS were proposed by the international ASAS working group in 2003 [1]. However, it is important to update such recommendations regularly in a rapidly evolving field of research. Therefore, it was decided at the time of publication that the first update would take place within two years. This paper describes the process and results of this update for use of anti-TNF therapy in AS.

Several aspects of anti-TNF therapy including the high costs make recommendations and guidelines mandatory. There is need to identify (i) patients with active disease, (ii) patients who are at risk of severe disease, (iii) patients with threatening functional disability, and (iv) patients who may have most benefit of anti-TNF therapy. Because limited data are available to answer these questions, the first consensus statement was developed by experts in the field based on data from research, clinical expertise, facilitated by a Delphi questionnaire and finalised in a formal consensus meeting to provide guidance for initiation, monitoring and discontinuation of anti-TNF therapy. These recommendations for anti-TNF therapy in AS are provided for use in clinical practice by rheumatologists. However, we hope that these recommendations are also adopted by other specialists involved in the treatment of patients with AS to ensure that patients with very active and severe disease obtain appropriate treatment from health care providers who have ample experience in treating AS patients with these drugs.
Methods

The manuscript of the first publication in 2003 [1] served as basis for this paper. Publications from March 2003 onwards were extracted and data are added to this present report. All members of the ASAS international working group received a questionnaire to obtain input on the various aspects of the published recommendations. The results of this questionnaire were presented during a workshop of the ASAS working group on January 21st and 22nd 2005 in Amsterdam, the Netherlands. Discussion among the participants led to the changes in the consensus statement and recommendations as presented in this manuscript. The ASAS workshop is organised under auspices of the ASAS Steering Committee.

As with the first manuscript, the systematic order followed in the publication of the British National Institute for Clinical Excellence (NICE) has been used in large parts of this manuscript [2] and in line with the AGREE instrument [3] this paper intends to define the scope, purpose, and potential health impact of the consensus statement.
Results

I. Background informations and general statements

1. General recommendations

The recommendations are for patients with AS but may be followed for severe early forms and very active patients who do not meet the established New York criteria [4-6].

Infliximab and etanercept are both recommended as options for the treatment of patients with active ankylosing spondylitis who are not satisfactorily treated conventionally with non-steroidal anti-inflammatory drugs (NSAIDs) [7-12]. It is expected that adalimumab may be effective but data are limited [13] and it has not been registered for the use in AS to date.

The use of these agents and follow-up of response should be undertaken only by an experienced health care provider such as a rheumatologist specialised in their use. The choice of the anti-TNF drug should be determined by consultation between patient and physician, taking into account differences in treatment schedules and patient preferences. A history of chronic inflammatory bowel disease should influence the decision of the anti-TNF agent (for further details see below). Maintenance therapy with infliximab should be at the lowest licensed dose compatible with continuing clinical response. Although most patients seem to need the licensed dose of 5mg/kg given i.v. in an interval of 6 weeks there are some patients who benefit from 3mg/kg every 8 weeks – as approved for rheumatoid arthritis (RA) together with methotrexate (see also below). Etanercept is given weekly in a fixed dosage.

It is recommended and strongly encouraged that all clinicians prescribing these agents should preferably register patients on TNF-blocker therapy in a national register to collect information on outcome and toxicity of anti-TNF agents.

There are some weak predictors of response to anti-TNF therapy [14]. On a group level, patients with younger age and shorter disease duration seem to do somewhat better, but these factors are too inadequate to apply in clinical practice in an individual patient. Contribution of MRI and CRP is even less strong [15], and initial BASDAI or BASFI values are not predictive of response. However, overall there are too limited data to make a final statement on the prediction of response to anti-TNF therapy.

At the moment there is limited evidence to support long-term treatment beyond 2 or more years. For infliximab there is evidence of efficacy and safety for up to 3 years [16], for etanercept up to 2 years [17]. Data for longer term therapy are expected but are not yet available. Withdrawal of anti-TNF therapy after years of continuous treatment frequently leads to clinical relapses [18, 19].

The evidence for consecutive use of the different agents is limited. Similar to RA, switching from one anti-TNF agent to another has been done but there is limited experience. Early reports on limited patient numbers suggest that the switch is possible and partly successful (unpublished observations). Published instruments should be used for monitoring of the disease [20, 21].
2. The technologies

Tumour necrosis factor α (TNFα) is a pro-inflammatory mediator that has been identified as an important molecule in the pathogenesis of AS and related SpA. Abundant messenger RNA of TNFα has been detected in the sacroiliac joints of AS patients [22]. The drug profiles have been described in detail in the original recommendations [1].

**Infliximab** in a dosage of 5mg/kg given every 6-8 weeks has been approved for the treatment of signs and symptoms of patients with active AS, Crohn’s disease, psoriasis and psoriatic arthritis in Europe and the U.S. Similarly, approval has been obtained for other unrelated rheumatic diseases such as RA and juvenile RA. In contrast to RA, infliximab is registered as monotherapy for AS.

**Etanercept** in a dosage of 25mg biweekly given as subcutaneous injection has been approved for the treatment of signs and symptoms of patients with active AS, psoriasis and psoriatic arthritis in Europe and the U.S. Similarly, approval has been obtained for other unrelated rheumatic diseases such as RA and juvenile RA.

**Adalimumab** in a dosage of 40mg given every other week as subcutaneous injection is approved for RA in Europe and the U.S but not for AS at present. There is only an open pilot study suggesting its benefit in AS with a dose of 40 mg every other week [13]. Double-blind randomised clinical trials are ongoing.

3. Clinical Effectiveness in AS

Data on clinical effectiveness have recently been extensively reviewed [23]. All important initial studies have been referenced in the first manuscript [1]. The more recent studies providing additional evidence are listed below. The clinical efficacy of infliximab and etanercept is substantiated by studies using magnetic resonance imaging [24-26] showing a clear reduction of acute inflammation in the spine and the sacroiliac joints.

a. Infliximab [10, 15, 16, 18]
b. Etanercept [7, 8, 25-27]
c. Adalimumab [13]; (two RCTs ongoing)

4. Cost Effectiveness

There is substantial evidence from the RCTs that the quality of life of AS patients treated with anti-TNF therapy is increased to a relevant extent for the patients. There are early hints that an influence of socio-economic parameters is likely [28]. Costs per QALYs have been calculated suggesting the cost effectiveness of the compound [29]. In that study, the cost of treatment with infliximab was found to be partly offset by reductions in the cost of the disease, leading to a cost per QALY gained in the vicinity of 20,000 - 30,000 € in the short term, but potentially below 7500 € in the long term. However, more data are clearly needed to fully answer this question.
5. Considerations

1. The results of the available clinical trials provide strong evidence of the clinical effectiveness of infliximab and etanercept, and are supported by data on continuation of treatment of up to 3 years. In contrast to RA, no DMARDs are known to have beneficial efficacy in AS for axial disease [23].

2. The optimal dosages of both agents are somewhat uncertain for both compounds since no direct comparative studies have been performed. For infliximab, dosage of 3mg/kg and 5mg/kg and treatment intervals between 6 weeks and 14 weeks have been used. At present, most data are available for the dosage of 5mg/kg every 6 weeks. However, lower dosages and longer intervals may also work in subgroups of patients and the value of adding an immunosuppressant such as methotrexate or azathioprine, as has been discussed in Crohn’s disease [30], to increase the effects of infliximab is as yet unclear [31].

3. No clear advantage of either agent has been substantiated. The lack of efficacy of etanercept in Crohn’s disease [32] suggests that ethanercept should not be the first choice in AS patients with concomitant Crohn’s. There are even some hints that etanercept may trigger flares of underlying Crohn’s disease [27]. There is strong evidence that Infliximab is effective in Crohn’s disease for colitis [30, 33]. There is one small study showing efficacy for arthritis in patients with Crohn’s disease associated with spondylarthitis [34]. Both agents were shown to work in psoriasis and in patients with psoriatic arthritis, all in randomised controlled trials [35-37]. There is some efficacy also in patients with undifferentiated SpA [38, 39], but data are still limited.

6. Implications

Using conservative estimates of the AS prevalence of 0.1% an estimated 600,000 people in Europe and at least 500,000 in the US have AS. On the basis of available data banks about a third of these patients have severe disease. Thus, more than 1,000,000 European and US patients with AS are potential candidates for this treatment. The numbers of patients with contraindications against this therapy (in RA 15%), the patients who do not respond to this therapy and the patients who withdraw due to other reasons (in AS about 20% in the first year) have to be subtracted, when calculating the number of patients for continuous treatment. The differences in the way of application between infliximab and etanercept also need to be mentioned in this regard since infliximab is infused while etanercept may be self-injected. Thus, a greater demand for day-care facilities can be expected for treatment with infliximab. The patients seem to have no clear-cut favourable mode of application [unpublished observation]. The current drug costs are still a major factor in the decision making process of rheumatologists all over the world.

7. Further research

The long-term impact of anti-TNF therapy in AS is unclear at present. There is need to further study the effects of anti-TNF therapy on radiological progression. A reduced risk of joint damage and disability may reduce the frequency of hip joint replacements and other types of surgery. The possibility of discontinuation of therapy after long-lasting benefit [18] needs to be further studied. Whether addition of immunosuppres-
sants may decrease the need for high doses and short intervals of therapy with infliximab [31] needs further study. The use of biologic registries is highly recommended.

8. Implementation

Clinicians treating AS patients should review their current practice in line with the guidance provided in this manuscript. Each patient treated should be documented and recorded.

These recommendations are published in the official journal of the EULAR and they are available on the website of the Annals of Rheumatic Diseases www.EULAR.org and on the ASAS website www.asas-group.org.
II. Results from the questionnaire

Fifty-one percent of the ASAS members (37/72) responded to the questionnaire. 87% of the participants used the criteria in clinical practice and stated that these were helpful. Fewer members believed that the criteria were also helpful in negotiations with payers (66%). Also, 66% considered the criteria would be accepted in their country by rheumatologists. In contrast, only 50% of the participants were fully satisfied with the present recommendations and 55% proposed some changes to be made. During the ASAS-meeting in Amsterdam each aspect of the recommendations was reviewed and the audience discussed and voted if, and if yes, what should be changed. In the end, there were only very minor changes to the published recommendations. The discussion and these changes are reported here. The full recommendations are presented in the Table.

III. Consensus Guidance for Treatment of Ankylosing Spondylitis with Biologic Agents

1. Diagnosis

Again, there was agreement that patients with a definite diagnosis of ankylosing spondylitis by the modified New York criteria should be applied. However, it was recognized that there is a wider range of spondyloarthritides (SpA), especially early forms of undifferentiated SpA (uSpA) with predominant axial involvement [5, 6] and/or other manifestations, which are not covered by these criteria and which might also benefit from treatment with anti-TNF therapy. There is a potential for modern imaging techniques such as magnetic resonance imaging (MRI) and ultrasound (US) to establish a diagnosis of SpA earlier but there has been no general consensus on that and those techniques have not been used in the trials for that purpose.

2. Disease activity

After some discussion it was confirmed that, for the assessment of disease activity, both the BASDAI and an expert opinion are required. Moreover, the cut-off of the BASDAI ≥ 4 for active disease and the definition of the expert opinion were also confirmed. It was discussed if active MRI or an elevated CRP as objective signs of inflammation could be mandatory to start anti-TNF therapy. However, clear data supporting such a strategy are lacking. The only data that are available so far do not support this for individual patients [18].

3. Failure of standard treatment

Most discussion and changes occurred in this part of the recommendations. Although, the general idea did not change, participants felt that a clarification of the recommendations would be helpful. It was intended in the first consensus statement that patients who receive anti-TNF therapy for axial symptoms do not need to be treated with DMARDs such as sulfasalazine and methotrexate before the initiation of treatment. This is now explicitly stated in the table. Moreover, the wording of using corticosteroid injections for peripheral arthritis was changed slightly. For patients with peripheral arthritis, treatment with sulfasalazine is a prerequisite. However, there was
near full agreement that the use of methotrexate in these patients should not be a prerequisite. As current evidence is lacking to support local corticosteroid injections for enthesitis, this statement was changed into 'must have failed appropriate local treatment'.

4. Contraindications

No specific changes were recommended for this part. But participants felt it important to add a part on pregnancy. There is limited information on fathering a child and on pregnancy during the use of anti-TNF therapy. However, based on one publication [40] and on post-marketing surveillance, outcome of pregnancy while one of the parents was using anti-TNF therapy does not seem to be different from what would have been expected. It should be noted that regulatory agencies do state to wait six months after the last dose before planning a pregnancy [40].

5. Monitoring and withdrawal

No changes were made to the recommendations for monitoring and withdrawal of treatment due to lack of response.
Conclusions

This is the first update on the 2003 consensus statement on the initiation, monitoring, and withdrawal of anti-TNF therapy in AS. Overall, there was a good acceptance of the published consensus statement and recommendations among the ASAS-experts. Although about half of the participating ASAS members suggested some changes when asked by questionnaire, only very few changes were felt to be necessary after discussion during a consensus meeting.

It is hoped that this consensus will again be widely accepted and implemented. The consensus is the product of a multinational committee who has a dedicated interest in treating patients with AS. There will be another evaluation and update published within another two years.

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### Specification (definition of the terms)

#### Patient Selection

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>- Patients normally fulfilling modified New York Criteria for definitive AS</td>
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<tr>
<td></td>
<td>- Modified New York criteria 1984 (4)</td>
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<tr>
<td></td>
<td>- <strong>Radiological criterion</strong></td>
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<tr>
<td></td>
<td>- Sacroiliitis, grade ≥ II bilaterally or grade III to IV unilaterally</td>
</tr>
<tr>
<td></td>
<td>- <strong>Clinical criteria</strong> (2 out of the following 3)</td>
</tr>
<tr>
<td></td>
<td>- Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest</td>
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<tr>
<td></td>
<td>- Limitation of motion of the lumbar spine in both the sagittal and frontal planes</td>
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<tr>
<td></td>
<td>- Limitation of chest expansion relative to normal values correlated for age and sex</td>
</tr>
<tr>
<td><strong>Active disease</strong></td>
<td>- Active Disease for ≥ 4 weeks</td>
</tr>
<tr>
<td></td>
<td>- BASDAI ≥ 4 (0-10) and an expert* opinion**</td>
</tr>
<tr>
<td></td>
<td>*The expert is a physician, usually a rheumatologist, with expertise in inflammatory back pain and the use of biologics. Expert should be locally defined.</td>
</tr>
<tr>
<td></td>
<td>**The expert should consider clinical features (history and examination), serum acute phase reactant levels and/or imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating ongoing inflammation.</td>
</tr>
<tr>
<td><strong>Treatment failure</strong></td>
<td>- All patients should have had adequate therapeutic trials of at least 2 NSAIDs. An adequate therapeutic trial is defined as:</td>
</tr>
<tr>
<td></td>
<td>- Treatment for at least 3 months at maximal recommended or tolerated anti-inflammatory dose unless contraindicated</td>
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<tr>
<td></td>
<td>- Treatment for &lt; 3 months where treatment was withdrawn because of intolerance, toxicity, or contraindications.</td>
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<tr>
<td></td>
<td>- Patients with pure axial manifestations do not have to take DMARDs before anti-TNF therapy can be started.</td>
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<tr>
<td></td>
<td>- Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection if appropriate</td>
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<td></td>
<td>- Patients with persistent peripheral arthritis must have had a therapeutic trial of sulfasalazine*</td>
</tr>
<tr>
<td></td>
<td>- Patients with symptomatic enthesitis must have failed appropriate local treatment.</td>
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<tr>
<td></td>
<td>*Sulfasalazine: Treatment for at least 4 months at standard target dose or maximally tolerated dose unless contraindicated or not tolerated. Treatment for less than 4 months, where treatment was withdrawn because of intolerance or toxicity or contraindicated.</td>
</tr>
<tr>
<td><strong>Contraindication</strong></td>
<td>- Women who are pregnant or breastfeeding; effective contraception must be practiced</td>
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<tr>
<td></td>
<td>- Active infection</td>
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<td></td>
<td>- Patients at high risk of infection including:</td>
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<td></td>
<td>- Chronic leg ulcer</td>
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<td></td>
<td>- Previous tuberculosis (note: please follow local recommendations for prevention or treatment)</td>
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<tr>
<td></td>
<td>- Septic arthritis of a native joint within the last 12 months</td>
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<tr>
<td></td>
<td>- Sepsis of a prosthetic joint within the last 12 months, or indefinitely if the joint remains in situ</td>
</tr>
</tbody>
</table>

*The expert is a physician, usually a rheumatologist, with expertise in inflammatory back pain and the use of biologics. Expert should be locally defined.*

**The expert should consider clinical features (history and examination), serum acute phase reactant levels and/or imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating ongoing inflammation.*
- Persistent or recurrent chest infections
- Indwelling urinary catheter
- History of Lupus or Multiple Sclerosis
- Malignancy or pre-malignancy states excluding:
  - Basal cell carcinoma
  - Malignancies diagnosed and treated more than 10 years previously (where the probability of total cure is very high)

### Assessment of Disease

<table>
<thead>
<tr>
<th>ASAS core set for daily practice</th>
<th>Physical function (BASFI or Dougados functional index)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain (VAS, last week, spine at night, due to AS and VAS, last week, spine due to AS)</td>
</tr>
<tr>
<td></td>
<td>Spinal mobility (chest expansion and modified Schober and occiput to wall distance and lateral lumbar flexion)</td>
</tr>
<tr>
<td></td>
<td>Patient’s global assessment (VAS, last week)</td>
</tr>
<tr>
<td></td>
<td>Stiffness (duration of morning stiffness, spine, last week)</td>
</tr>
<tr>
<td></td>
<td>Peripheral joints and entheses (number of swollen joints [44 joints count], enthesitis score such as developed in Maastricht, Berlin or San Francisco)</td>
</tr>
<tr>
<td></td>
<td>Acute phase reactants (ESR or CRP)</td>
</tr>
<tr>
<td></td>
<td>Fatigue (VAS)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>BASDAI</th>
<th>VAS overall level of fatigue/tiredness past week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VAS overall level of AS neck, back, or hip pain past week</td>
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<tr>
<td></td>
<td>VAS overall level of pain/swelling in joints other than neck, back or hips past week</td>
</tr>
<tr>
<td></td>
<td>VAS overall discomfort from any areas tender to touch or pressure past week</td>
</tr>
<tr>
<td></td>
<td>VAS overall level of morning stiffness from time of awakening past week</td>
</tr>
<tr>
<td></td>
<td>Duration and intensity (VAS) of morning stiffness from time of awakening (up to 120 minutes)</td>
</tr>
</tbody>
</table>

### Assessment of Response

<table>
<thead>
<tr>
<th>Responder criteria</th>
<th>BASDAI:50% relative change or absolute change of 20 mm (on a scale between 0 and 100) and Expert Opinion in favor of Continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of evaluation</td>
<td>Between 6 and 12 weeks</td>
</tr>
</tbody>
</table>

VAS=visual analogue scale; all VAS can be replaced by a NRS= numerical rating scale

We acknowledge the contributions of the following ASAS members who either participated in the meeting and/or completed the questionnaires. The ASAS working group is financially supported by unrestricted grants from Abbott, Amgen, Centocor, Merck, Schering Plough, and Wyeth. The consensus meeting was organised under auspices of the steering committee of ASAS.
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