2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis

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ABSTRACT

This paper presents the second update of the Assessment in SpondyloArthritis international Society (ASAS) consensus statement on the use of anti-tumour necrosis factor (anti-TNF) agents in patients with axial spondyloarthritis (SpA). A major change from the previous recommendations is that patients fulfilling the ASAS axial SpA criteria, which also include patients fulfilling the modified New York criteria for ankylosing spondylitis, can be treated with anti-TNF agents. This makes an earlier start in the disease process possible. A second major change is the mandatory pretreatment before anti-TNF agents can be started. All patients should have tried a minimum of two non-steroidal anti-inflammatory drugs for a minimum of 4 weeks in total. This is significantly shorter than the previous requirement of 3 months. As previously, patients with axial symptoms require no further pretreatment. Patients with symptomatic peripheral symptoms should normally have had an adequate therapeutic trial of a disease-modifying antirheumatic drug, preferably sulfasalazine. Sulfasalazine is no longer mandatory in this group of patients. Finally, efficacy should be evaluated after at least 12 weeks. The remaining recommendations stayed largely unchanged.

INTRODUCTION

In 2003 a consensus statement on the use of anti-tumour necrosis factor (anti-TNF) agents was published by the Assessment in SpondyloArthritis international Society (ASAS).[1] This was followed by an update in 2006.[2] In 2009 a second update was undertaken to include new developments in the field. Since the field is rapidly moving, the recommendations need to be updated regularly. Together with the update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis (AS), an update of the recommendations for the use of anti-TNF agents was performed.[3]

METHODS

The manuscript of the first update served as the basis for this second update. The following information was collected: (1) data from the literature on the management of AS since the 2006 update; (2) data from a survey of 1242 rheumatologists from 18 countries; (3) national guidelines in 23 countries. The detailed information on the survey is published as an appendix to this paper (supplementary online appendix); the other two—data from the literature and national guidelines—will be published separately. All this information was presented to the members of ASAS during the annual workshop in Rome in January 2009 and the ASAS workshop in June 2009 in Copenhagen. Each recommendation was presented with the relevant information from the three sources mentioned above. Thereafter there was an open discussion, followed by voting on the question if a change was needed. If there was a majority vote that a change was needed, new concepts and new wording were discussed and proposed for voting. Wording was changed until a majority was in favour of that specific wording. As with the previous consensus document, the recommendations from the Appraisal of Guidelines Research and Evaluation instrument were followed.[4]

RESULTS

Table 1 compares the 2006 recommendations with the recommendations from this update. The changes are highlighted. Table 2 presents the 2010 recommendations.

Diagnosis

The existing recommendation was to treat patients 'normally' fulfilling the modified New York criteria.[5] Answers to the questionnaire, however, showed that practising rheumatologists considered this to be a barrier (supplementary online appendix). More than 60% of the respondents would like the option to diagnose AS according to MRI findings. This was largely echoed by the ASAS membership: 94% voted in support of the option to use MRI and/or CT as an imaging method. In a follow-up question, 81% voted for the ASAS axial spondyloarthritis (SpA) criteria as additional criteria for making the diagnosis of SpA. In fact, all patients fulfilling the modified New York criteria for AS will also fulfil the ASAS criteria for axial SpA.[6] Nevertheless, it was felt clearer, at least for the time being, to keep both the modified New York criteria as well as the ASAS axial SpA criteria in the recommendation for diagnosis. One of the main reasons for this large support to open the option to treat patients with axial SpA not fulfilling the modified New York criteria is that this is mainly seen as an early stage of the same disease spectrum.[7] And importantly, it has been shown that patients with axial SpA not fulfilling the modified New York criteria have similar burden of disease as patients fulfilling these

Table 1 Changes between the first and second update of the recommendations for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis

Comparison of first and second update of recommendations; changes highlighted in ***italic bold***	
2006 Update recommendations	**2010 Update recommendations**
Diagnosis	**Diagnosis**
Patients normally fulfilling modified New York criteria for definitive ankylosing spondylitis	Patients fulfilling modified New York criteria for definitive ankylosing spondylitis ***or the ASAS criteria for axial SpA***
Active disease	**Active disease**
Active disease for ≥4 weeks BASDAI≥4 (0–10) and positive expert opinion	Active disease for ≥4 weeks BASDAI≥4 (0–10) and positive expert opinion
Treatment failure	**Treatment failure**
All patients: should have had adequate therapeutic trials of at least two NSAIDs; defined as for at least 3 months at maximum recommended dose unless contraindicated; <3 months in cases of intolerance, toxicity **Axial disease:** no pretreatment with DMARDs required **Peripheral arthritis:** one local corticosteroid injection if appropriate; therapeutic trial of sulfasalazine (4 months maximum tolerated dose) mandatory **Enthesitis:** appropriate local treatment	**All patients:** should have had adequate therapeutic trial of at least two NSAIDs; ***defined as at least two NSAIDs over a 4-week period*** in total at maximum recommended dose unless contraindicated; **Axial disease:** no pretreatment with DMARDs required **Peripheral arthritis:** one local corticosteroid injection if appropriate; ***should normally have had a therapeutic trial of a DMARD, preferably sulfasalazine*** **Enthesitis:** appropriate local treatment
Contraindications	**Contraindications**
List of contraindications	***Refer to annually updated consensus statement on biological agents***
Assessment of disease	**Assessment of disease**
ASAS core set for daily practice and BASDAI	ASAS core set for daily practice and BASDAI
Assessment of response	**Assessment of response**
50% Improvement in BASDAI or absolute change of 2 (0–10) and positive expert opinion in favour of continuation Assessment between 6 and 12 weeks	50% Improvement in BASDAI or absolute change of 2 (0–10) and positive expert opinion in favour of continuation ***Assessment after at least 12 weeks***

ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthritis.

Table 2 2010 Update of recommendations for the use of anti-tumour necrosis factor agents in patients with axial SpA (including AS)

	Recommendation
Patient selection	
Diagnosis	► Patients fulfilling modified New York Criteria for definitive AS* or the ASAS criteria for axial SpA†
Active disease	► Active disease for ≥4 weeks ► BASDAI ≥ 4 (0–10)‡ and a positive expert opinion§
Treatment failure	► **All patients** should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as at least two NSAIDs over a 4-week period in total at maximum recommended or tolerated anti-inflammatory dose unless contraindicated ► **Patients with predominantly axial manifestations** do not have to take DMARDs before anti-TNF treatment can be started ► **Patients with symptomatic peripheral arthritis** should have an insufficient response to at least one local steroid injection if appropriate and should normally have had adequate a therapeutic trial of a DMARD, preferably sulfasalazine ► **Patients with symptomatic enthesitis** must have failed appropriate local treatment
Assessment of disease	
ASAS core set for daily practice and BASDAI	
Assessment of response	
Responder criteria	► BASDAI: 50% relative change or absolute change of 2 (on 0–10 scale) *and* expert opinion in favour of continuation
Time of evaluation	► After at least 12 weeks

*Modified New York criteria (van der Linden *et al*, 1984): Radiological criterion (sacroiliitis, grade ≥II bilaterally or grade III to IV unilaterally) and at least two out of three clinical criteria (low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest; limitation of motion of the lumbar spine in both the sagittal and frontal planes; limitation of chest expansion relative to normal values correlated for age and sex).[5]
†See figure 1 for the ASAS axial SpA criteria.[6]
‡BASDAI assessed on a 0–10 VAS or NRS.[14]
§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. An expert opinion should consider clinical features (history and examination) as well as either serum acute phase reactant levels or imaging results, such as radiographs demonstrating rapid progression or MRI scans indicating inflammation.
ASAS core set for daily practice: physical function (BASFI); Pain (VAS/NRS, last week, spine at night, due to AS and VAS/NRS, last week, spine due to AS); spinal mobility (chest expansion, cervical rotation, occiput-to-wall distance, modified Schober, and (lateral lumbar flexion or BASMI); patient's global assessment (VAS/NRS, last week); stiffness (duration of morning stiffness, spine, VAS/NRS, last week); peripheral joints and entheses (number of swollen joints (44 joints count), enthesitis score such as developed in Maastricht, Berlin or San Francisco); acute phase reactants (preferably CRP); fatigue (VAS/NRS).
AS, ankylosing spondylitis; ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthritis; TNF, tumour necrosis factor; VAS, visual analogue scale.

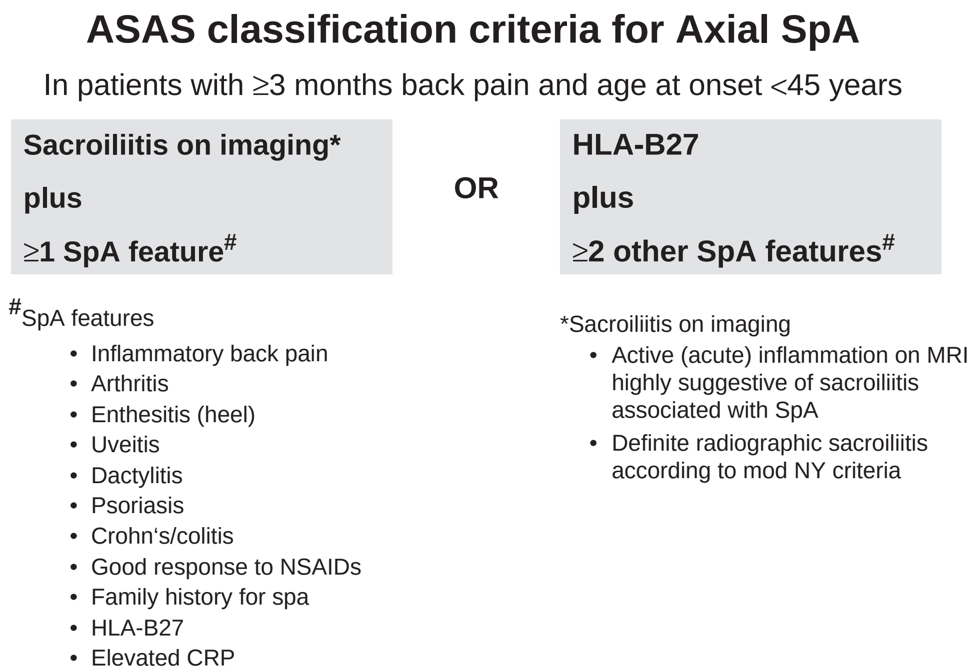

Figure 1 ASAS classification criteria for axial spondyloarthritis (SpA).[6] CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs.

criteria.[8] Finally, studies with TNF blockers in patients with axial SpA show at least similar efficacy to, and, in part, clearly better efficacy than, studies in patients fulfilling modified New York criteria.[9 10]

Active disease

Eighty-six per cent of the respondents to the questionnaire agreed conceptually with the choice of the criteria to define active disease (a score of ≥7 on a 0–10 scale). Among the ASAS membership, 78% voted to keep the criteria unchanged, which was the final decision for this recommendation.

Previous treatment

Seventy-six per cent of the ASAS membership voted to change the recommendation on the specifics of pretreatment before a patient may start a TNF blocker. First, the use of non-steroidal anti-inflammatory drugs (NSAIDs) was discussed. A total of 76% of the membership wanted to change the recommendation as follows: keep the minimum number of NSAIDs that have been tried at two, but shorten the period. We searched the literature to determine the length of time beyond which it would be unlikely that an NSAID would be effective. Only a few trials provided detailed information on the time course of efficacy, but these show that the maximum effect is achieved after 2 weeks.[11 12] In the end, it was decided that a minimum of two NSAIDs should be tried for a minimum of 4 weeks in total. This leaves some flexibility on how long to use each NSAID and prevents a patient continuing with an ineffective NSAID and having the risk of adverse events without a possible benefit. So the use of one NSAID for 1 week and another for 3 weeks, as well as two NSAIDs for 2 weeks would each fulfil this criterion. Failure of an NSAID is defined as insufficient efficacy while the drug is being used.

The recommendation that no pretreatment with any disease-modifying antirheumatic drug (DMARD) is required in patients with predominantly axial disease was fully supported and remained unchanged. In contrast, only 9% of the membership wanted to keep the DMARD recommendation in patients with predominantly peripheral disease unchanged. Thirteen per cent voted to keep sulfasalazine as mandatory pretreatment but for a shorter period. While 48% voted to exclude pretreatment with any DMARD altogether, 30% voted in favour of using one unspecified DMARD. The updated literature review did not reveal any studies evaluating the efficacy of DMARDs other than sulfasalazine in patients with peripheral arthritis, whereas in the previous review of the literature we found studies showing the lack of efficacy of DMARDs such as methotrexate and leflunomide. The final decision was to leave the decision on pretreatment in patients with predominantly peripheral arthritis more flexible. It was regarded as reasonable to use one DMARD agent and that although evidence still supports a preference for sulfasalazine this is not regarded as fundamental.

The pretreatment for patients predominantly with enthesitis did not change.

Contraindications

In the previous recommendations, a list of contraindications was included. In this update it was decided to leave this out, but refer to the previous consensus statement for AS and to general recommendations. The main reason is that there are only a limited number of absolute contraindications, but in most situations extra care needs to be taken in relation to comorbidity, concurrent (prophylactic) medication and monitoring. Although there was a high level of agreement with the individual contraindications (ranging from 7.9 to 9.8), it was apparent that rheumatologists use a variety of contraindications that differ from those listed (confirmed by 27% of the rheumatologists) and do not always apply the contraindications from the list. Also the national recommendations provide a wide range of contraindications that differ from the previously recommended list. Moreover, as the current recommendations for AS are updated only every few years, these are not the best place in which to keep up to date on new safety concerns. Finally, most safety issues are not specific for AS. Therefore, it is recommended that the annually updated consensus statement on the use of biological agents should be consulted.[13]

Assessment of disease

No change was suggested for how to assess disease activity and severity. This should still be based on the measures included in the ASAS core set for daily practice and the Bath Ankylosing Spondylitis Disease Activity Index.[14 15]

Assessment of response

The assessment of response was not changed. However, the time of evaluation was lengthened from between 6 and 12 weeks previously to beyond 12 weeks. In phase III trials of anti-TNF agents treatment response rates plateau from 12 weeks onwards and so the evidence favours at least 12 weeks of continuous treatment before deciding on the desirability of continuing treatment.

DISCUSSION

This is the second update of the international consensus statement of the use of anti-TNF agents in AS. Although the majority of the recommendations remain largely unchanged, the suggested changes have major implications. The first and most important change is that from now on patients who fulfil the ASAS axial SpA criteria can also be treated with anti-TNF agents according to these recommendations. This means that patients with changes in the sacroiliac joints on MRI but not fulfilling the grading of the sacroiliac joints on radiographs ('non-radiographic axial SpA' vs 'radiographic axial SpA') satisfy the criteria for the start of a TNF blocker. This will make an earlier start of anti-TNF treatment in the disease course possible. As the burden of the disease is similar between patients with non-radiographic and radiographic axial SpA, and the efficacy of anti-TNF treatment is at least similar, this is a logical step. Anti-TNF agents do not inhibit the progression of syndesmophytes in patients with established AS over a 2-year period.[16–18] Long-term evaluation should prove if this earlier start will also have a positive effect on progression of structural damage and prevention of long-term disability.

A second major change is in the specifics of the required pretreatment: an insufficient response to at least two NSAIDs during a total 4-week period is satisfactory to fulfil the NSAID pretreatment requirement. Moreover, in patients with predominantly peripheral disease, treatment with sulfasalazine is no longer considered mandatory.

Finally, the treatment period should be at least 12 weeks before the success or otherwise of the anti-TNF therapy is judged. Altogether, these recommendations provide an option for using anti-TNF treatment on a wider scale. This is supported by new developments over the past few years. Among these are the options to make an earlier diagnosis by the ASAS axial SpA criteria, and the effectiveness and safety of anti-TNF treatment in this patient population. We hope that these international recommendations will again form the basis for national recommendations and achieve widespread implementation.

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Notes