EXTENDED REPORT

First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis

J Braun, J Davis, M Dougados, J Sieper, S van der Linden, D van der Heijde, for the ASAS Working Group

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See end of article for authors' affiliations

Correspondence to: Prof Dr J Braun, Rheumazentrum Ruhrgebiet, Landgrafenstr 15, 44652 Herne, Germany; J.Braun@rheumazentrum-ruhrgebiet.de

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Objective: To update the international recommendations for use of anti-tumour necrosis factor (TNF) agents in the treatment of ankylosing spondylitis.
Methods: The published recommendations on anti-TNF treatment in ankylosing spondylitis formed the basis of the update. A questionnaire was sent to the ASAS (assessment in ankylosing spondylitis) members before the final decisions were agreed upon at an international meeting of the ASAS working group.
Results: Only minor changes to the original consensus statement were required. For the *initiation* of anti-TNF treatment, there should be: a diagnosis of definitive ankylosing spondylitis (normally based on modified New York criteria); active disease for at least four weeks, as defined by a sustained Bath ankylosing spondylitis disease activity index (BASDAI) of $\geqslant$4 on a 0–10 scale and expert opinion based on clinical findings; refractory disease, defined by failure of at least two non-steroidal anti-inflammatory drugs during a three month period, failure of intra-articular steroids (if indicated), and failure of sulfasalazine in patients with predominantly peripheral arthritis; and application of the usual precautions and contraindications for biological treatment. For *monitoring* anti-TNF treatment: both the ASAS core set for clinical practice and the BASDAI should be followed after the initiation of treatment. *Discontinuation* of anti-TNF treatment in non-responders should be considered after 6–12 weeks. *Response* is defined by improvement of at least 50% *or* 2 units (on a 0–10 scale) of the BASDAI.
Conclusions: This updated consensus statement is recommended in guiding clinical practice and as a basis for developing national guidelines. Evaluation and regular update of this consensus statement is subject to further research by the ASAS group.

Anti-tumour necrosis factor (TNF) treatment is considered a major advance in the management of patients with ankylosing spondylitis. Recommendations for anti-TNF treatment in patients with ankylosing spondylitis were proposed by the international ASAS (assessment in ankylosing spondylitis) 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 treatment in ankylosing spondylitis.

Several aspects of anti-TNF treatment, including the high costs, make recommendations and guidelines mandatory. There is need to identify patients with active disease, patients who are at risk of severe disease, patients with threatening functional disability, and patients who may have most benefit from anti-TNF treatment. 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 and 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 treatment.

These recommendations for anti-TNF treatment in ankylosing spondylitis are provided for use in clinical practice by rheumatologists. However, we hope that they are also adopted by other specialists involved in the treatment of patients with ankylosing spondylitis, to ensure that those with very active and severe disease obtain appropriate treatment from health care providers who have ample experience in the use of 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 were added to the 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 21 and 22 January 2005 in Amsterdam, 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.

Abbreviations: AGREE, appraisal and guidelines for research and evaluation; ASAS, assessment in ankylosing spondylitis; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; DMARD, disease modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug; QALY, quality adjusted life year; TNF, tumour necrosis factor

RESULTS

Background information and general statements

General recommendations

The recommendations are for patients with ankylosing spondylitis but may be followed for severe early forms and for 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 ankylosing spondylitis 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 (for further details see below). Maintenance treatment with infliximab should be at the lowest licensed dose compatible with continuing clinical response. Although most patients seem to need the licensed dose of 5 mg/kg given intravenously in an interval of six weeks, there are some who benefit from 3 mg/kg every eight weeks—as approved for rheumatoid arthritis together with methotrexate (see also below). Etanercept is given weekly in a fixed dose.

It is recommended and strongly encouraged that all clinicians prescribing these agents should preferably register patients on TNF blocker treatment 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 treatment.[14] On a group level, patients of younger age and with shorter disease duration seem to do somewhat better, but these factors are too inadequate to apply in clinical practice in an individual patient. The contribution of magnetic resonance imaging (MRI) and C reactive protein is even less strong,[15] and the initial values of the Bath ankylosing spondylitis disease activity index (BASDAI) and the Bath ankylosing spondylitis functional index (BASFI) are not predictive of a response. However, overall there are too limited data to make a final statement on the prediction of response to anti-TNF treatment.

At present there is limited evidence to support long term treatment beyond two or more years. For infliximab there is evidence of efficacy and safety for up to three years,[16] and for etanercept up to two years.[17] Data for longer term treatment are expected but are not yet available. Withdrawal of anti-TNF treatment after years of continuous treatment often leads to clinical relapse.[18 19]

The evidence for consecutive use of the different agents is limited. As with rheumatoid arthritis, 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]

The technologies

Tumour necrosis factor α (TNFα) is a pro-inflammatory mediator that has been identified as an important molecule in the pathogenesis of ankylosing spondylitis and related SpA. Abundant messenger RNA of TNFα has been detected in the sacroiliac joints of patients with ankylosing spondylitis.[22]

The drug profiles were described in detail in the original recommendations.[1]

Infliximab in a dose of 5 mg/kg given every six to eight weeks has been approved for the treatment of signs and symptoms of patients with active ankylosing spondylitis, Crohn's disease, psoriasis, and psoriatic arthritis in Europe and the USA. Similarly, approval has been obtained for other unrelated rheumatic diseases such as rheumatoid arthritis and juvenile rheumatoid arthritis. In contrast to rheumatoid arthritis, infliximab is registered as monotherapy for ankylosing spondylitis.

Etanercept in a dose of 25 mg biweekly given as subcutaneous injection has been approved for the treatment of signs and symptoms of patients with active ankylosing spondylitis, psoriasis, and psoriatic arthritis in Europe and the USA. Similarly, approval has been obtained for other unrelated rheumatic diseases such as rheumatoid arthritis and juvenile rheumatoid arthritis.

Adalimumab in a dose of 40 mg given every other week by subcutaneous injection is approved for rheumatoid arthritis in Europe and the USA, but not for ankylosing spondylitis at present. There is only one open pilot study suggesting that it is of benefit in ankylosing spondylitis at a dose of 40 mg every other week.[13] Double blind randomised clinical trials are ongoing.

Clinical effectiveness in ankylosing spondylitis

Data on clinical effectiveness have recently been extensively reviewed.[23] All important initial studies were cited in the first manuscript.[1] More recent studies are available providing additional evidence on infliximab,[10 15 16 18] etanercept,[7 8 25–27] and adalimumab.[13] For the latter, two randomised controlled trial are ongoing. The clinical efficacy of infliximab and etanercept is substantiated by studies using MRI,[24–26] showing a clear reduction in acute inflammation in the spine and sacroiliac joints.

Cost-effectiveness

There is substantial evidence from the randomised controlled trial that the quality of life in patients with ankylosing spondylitis treated with anti-TNF treatment is increased to a useful extent. There are early hints that an influence of socioeconomic variables is likely.[28] Costs per QALY (quality adjusted life year) 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 answer this question fully.

Considerations

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 for up to three years. In contrast to rheumatoid arthritis, no disease modifying antirheumatic drugs are known to have a beneficial effect on axial disease in ankylosing spondylitis.[23]

The optimal doses of both agents are somewhat uncertain as no direct comparative studies have been undertaken. For infliximab, a dose of between 3 mg/kg and 5 mg/kg and treatment intervals between six and 14 weeks have been used. At present, most data are available for the dosage of 5 mg/kg every six weeks. However, lower doses 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 effect of infliximab is as yet unclear.[31]

No clear advantage of either agent has been substantiated. The lack of efficacy of etanercept in Crohn's disease[32] suggests that this drug should not be the first choice in patients with ankylosing spondylitis with concomitant Crohn's disease. 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 spondyloarthritis.[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 spondyloarthropathy,[38 39] but data are still limited.

Implications

Using conservative estimates of the ankylosing spondylitis prevalence of 0.1%, an estimated 600 000 people in Europe and at least 300 000 in the USA have ankylosing spondylitis. On the basis of available data banks, about a third of these patients have severe disease. Thus more than a million European and American patients with ankylosing spondylitis are potential candidates for this treatment. The numbers of patients with contraindications to this treatment (in rheumatoid arthritis, 15%), those who do not respond to it, and those who withdraw for other reasons (in ankylosing spondylitis, about 20% in the first year) have to be subtracted when calculating the number of possible patients for continuous treatment.

The differences in the ways of administration between infliximab and etanercept also need to be mentioned in this regard as 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 favoured mode of administration (unpublished observations). The current drug costs are still a major factor in the decision making process of rheumatologists all over the world.

Further research

The long term impact of anti-TNF treatment in ankylosing spondylitis is unclear at present. There is need for further study of the effects of anti-TNF treatment on radiological progression. A reduced risk of joint damage and disability may lessen the frequency of hip joint replacements and other types of surgery. The possibility of discontinuation of treatment after long lasting benefit[18] needs to be further evaluated. Whether the addition of immunosuppressants may decrease the need for high doses and short treatment intervals with infliximab[31] needs further study.

The use of biological registries is highly recommended.

Implementation

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

These recommendations are published in the official journal of EULAR and are available on the website of the *Annals of Rheumatic Diseases* (www.EULAR.org) and on the ASAS website (www.asas-group.org).

Results from the questionnaire

Fifty one per cent of the ASAS members (37/72) responded to the questionnaire. Of these, 87% used the criteria in clinical practice and stated that they 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 that some changes should be made. During the ASAS meeting in Amsterdam each aspect of the recommendations was reviewed and the audience voted whether it should be changed. By 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 table 1.

Consensus guidance for treatment of ankylosing spondylitis with biological agents

Diagnosis

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

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, a BASDAI cut off of $\geqslant$4 for active disease and the definition of the expert opinion were also confirmed. It was discussed whether activity on MRI or a raised C reactive protein, as objective signs of inflammation, should be mandatory before starting anti-TNF treatment. 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]

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 treatment 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 table 1. Moreover, the wording relating to the use of 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 to ''must have failed appropriate local treatment.''

Contraindications

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

Table 1 Specification (definition of the terms)

PATIENT SELECTION	
Diagnosis	● Patients normally fulfilling modified New York criteria for definitive ankylosing spondylitis ● Modified New York criteria 1984[4] – *Radiological criterion*: Sacroiliitis, grade ⩾II bilaterally or grade III to IV unilaterally – *Clinical criteria* (two of the following three): low back pain and stiffness for more than three months which 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
Active disease	● Active disease for ⩾4 weeks ● BASDAI ⩾ 4 (0–10) and an expert* opinion†
Treatment failure	● All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as: – Treatment for at least 3 months at maximum recommended or tolerated anti-inflammatory dose unless contraindicated – Treatment for <3 months where treatment was withdrawn because of intolerance, toxicity, or contraindications ● Patients with pure 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 corticosteroid injection if appropriate ● Patients with persistent peripheral arthritis must have had a therapeutic trial of sulfasalazine‡ ● Patients with symptomatic enthesitis must have failed appropriate local treatment
Contraindications	● Women who are pregnant or breast feeding; effective contraception must be practised ● Active infection ● Patients at high risk of infection including: – Chronic leg ulcer – Previous tuberculosis (note: please follow local recommendations for prevention or treatment) – Septic arthritis of a native joint within the past 12 months – Sepsis of a prosthetic joint within the past 12 months, or indefinitely if the joint remains in situ – 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	
ASAS core set for daily practice	● Physical function (BASFI or Dougados functional index) ● Pain (VAS, past week, spine at night, from ankylosing spondylitis *and* VAS, past week, spine, from ankylosing spondylitis) ● Spinal mobility (chest expansion *and* modified Schober *and* occiput to wall distance *and* lateral lumbar flexion) ● Patient's global assessment (VAS, past week) ● Stiffness (duration of morning stiffness, spine, past 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 (ESR *or* CRP) ● Fatigue (VAS)
BASDAI	● VAS overall level of fatigue/tiredness, past week ● VAS overall level of ankylosing spondylitis neck, back, or hip pain, past week ● VAS overall level of pain/swelling in joints other than neck, back or hips, past week ● VAS overall discomfort from any areas tender to touch or pressure, past week ● VAS overall level of morning stiffness from time of awakening, past week ● Duration and intensity (VAS) of morning stiffness from time of awakening (up to 120 minutes)
ASSESSMENT OF RESPONSE	
Responder criteria	● BASDAI: 50% relative change *or* absolute change of 20 mm (on a scale between 0 and 100) *and* expert opinion in favour of continuation
Time of evaluation	● Between 6 and 12 weeks

*The expert is a physician, usually a rheumatologist, with expertise in inflammatory back pain and the use of biological agents. 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 indicating ongoing inflammation.
‡Sulfasalazine: treatment for at least four months at standard target dose or maximally tolerated dose unless contraindicated or not tolerated. Treatment for less than four months, where treatment was withdrawn because of intolerance or toxicity or contraindicated.
BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; CRP, C reactive protein; DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analogue scale (all VAS can be replaced by a numerical rating scale (NRS)).

Monitoring and withdrawal

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

CONCLUSIONS

This is the first update on the 2003 consensus statement on the initiation, monitoring, and withdrawal of anti-TNF treatment in ankylosing spondylitis. Overall, there was a good acceptance of the published consensus statement and recommendations among the ASAS experts. Although about half the participating ASAS members suggested some changes when asked by questionnaire, very few changes were felt necessary after discussions 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 which has a dedicated interest in treating patients with ankylosing spondylitis. Another evaluation and update will published in two years.

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Authors' affiliations

J Braun, Rheumazentrum Ruhrgebiet, Herne, and Ruhr University Bochum, Germany
J Davis, Division of Rheumatology, University of California San Francisco, California, USA

M Dougados, Department of Rheumatology, Hôpital Cochin, University of Paris, France
J Sieper, Medical Department I, Rheumatology, Benjamin Franklin Hospital, Free University Berlin, and German Rheumatism Research Centre Berlin, Germany
S van der Linden, D van der Heijde, Department of Internal Medicine, Division of Rheumatology, University of Maastricht, Netherlands

APPENDIX

LIST OF PARTICIPANTS/QUESTIONNAIRE COWORKERS

A Adebajo, UK; A Boonen, NL; FEJ van den Bosch, Belgium; J Brandt, Germany; J Braun; Germany*; R Burgos Vargas, Mexico; D Clegg, USA; E Collantes Estevez, Spain; J Darmawan, Indonesia; J Davis, USA*; BAC Dijkmans, NL; M Dougados, France*; T Duruöz, Turkey; J Edmonds, Australia; P Géher, Hungary; C Gonzalez-Fernandez, Spain; J Gu, China; F Guillemin, France; DMFM van der Heijde, NL*; I Horst van der Bruinsma, NL; F Huang, China; R Inman, Canada; L Gossec, France; MA Khan, USA; L Köhler, Germany; T Kvien, Norway; R Landewé, NL; SJ van der Linden, NL*; A Linssen, NL; J Listing, Germany; W Maksymowych, Canada; M Matucci-Cerinic, Italy; H Mielants, Belgium; I Olivieri, Italy; T Pham, France; J Reveille, USA; M Rudwaleit, Germany; C Salvarani, Italy; J Sieper, Germany*; MA Stone, Canada; R Sturrock, UK; R Valle, Columbia; K de Vlam, Belgium; U Weber, Switzerland; M Weisman, USA; H Zeidler, Germany.
*Steering Committee Members.

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