

2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis

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Accepted 14 March 2011

ABSTRACT

This first update of the ASAS/EULAR recommendations on the management of ankylosing spondylitis (AS) is based on the original paper, a systematic review of existing recommendations and the literature since 2005 and the discussion and agreement among 21 international experts, 2 patients and 2 physiotherapists in a meeting in February 2010. Each original bullet point was discussed in detail and reworded if necessary. Decisions on new recommendations were made — if necessary after voting. The strength of the recommendations (SOR) was scored on an 11-point numerical rating scale after the meeting by email. These recommendations apply to patients of all ages that fulfill the modified NY criteria for AS, independent of extra-articular manifestations, and they take into account all drug and non-drug interventions related to AS. Four overarching principles were introduced, implying that one bullet has been moved to this section. There are now 11 bullet points including 2 new ones, one related to extra-articular manifestations and one to changes in the disease course. With a mean score of 9.1 (range 8-10) the SOR was generally very good.

The European League against Rheumatism (EULAR) has developed management recommendations for various rheumatic conditions in the past decade¹⁻⁶ based on standard operating procedures published some years ago.⁷ The basis for the methodology is the AGREE instrument.⁸ A systematic literature review (SLR) serves as the basis for the expert discussions and the consensus process.⁹⁻¹¹ The Assessments in Ankylosing Spondylitis International Society (ASAS), which published a core set of endpoints for the disease more than 10 years ago¹² has taken the lead in developing recommendations for anti-tumour necrosis factor (TNF) therapy in ankylosing spondylitis (AS),¹³ which have already been updated twice.^{14 15} The two organisations jointly developed the first set of recommendations for the management of AS together in 2005.

As this is a requirement of the EULAR standard operating procedures for management recommendations and as the field of spondyloarthritis is moving rapidly, an update of the first recommendations for the management of AS is needed after 5 years.

While the first version of the management recommendations was initially developed without patients, and as discrepancies between patients'

and physicians' perspectives are well known,¹⁶ on this occasion patients were involved in the project group from the beginning. Moreover, other stakeholders, such as physiotherapists, were also represented in the project group. A patient-specific version of the first recommendations has been developed with the active support of patients of many European and North American countries.¹⁷ The original and the patient version of the recommendations has been evaluated^{18 19} and disseminated in several countries.²⁰⁻²³

AS is the prototype,²⁴ a subtype, and an outcome of spondyloarthritis, particularly of the axial form of spondyloarthritis. Recent new classification criteria have widened the spectrum of spondyloarthritis by including earlier forms in addition to AS.^{25 26} This project has also led to a separation in the classification to predominantly axial and peripheral forms of spondyloarthritis. The term 'axial spondyloarthritis' covers patients with chronic back pain who have AS, which is defined by the presence of definite structural changes on radiographs in the sacroiliac joints, and patients with early or abortive forms of spondyloarthritis, which is defined by the presence of sacroiliac inflammation as detected by MRI or the presence of HLA B27 in combination with the presence of features typical of spondyloarthritis.^{27 28} It can be anticipated that future trials will increasingly target axial spondyloarthritis rather than AS. Some trials with that aim have already been performed and some have started. However, as the evidence from such trials is currently limited it has been decided to restrict the recommendations to AS, although the project group unanimously agreed that these recommendations can equally be applied to patients with axial spondyloarthritis.

As the number of clinical trials and publications on AS therapy has steadily increased over the first decade of the millennium, this provided a sound rationale for a SLR.

METHODS

ASAS and EULAR agreed in 2009 to collaborate in the development of the first update of the recommendations. To facilitate the process, it was decided that the convenor (JB) and the epidemiologist (DvdH) would maintain the same role that they undertook in the development of the first recommendations.



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These original recommendations¹ formed the basis for the update. Two fellows performed the SLR, which needed an update since 2005 when the previous SLR was performed.¹¹ The international expert group included 21 rheumatologists, two orthopaedic surgeons, four patients (two of them were also rheumatologists) and one physiotherapist—representing 16 countries worldwide. The same group of international AS experts who participated in the development of the first recommendations was invited to participate.

The experts met on 15/26 February 2010 in Zurich. During the meeting, the data from the SLR dating from the previous search in 2005 until December 2009 were presented to the international experts. Each bullet point was discussed in detail until consensus was reached as to whether rewording was necessary. New recommendations were considered if this was proposed by a member of the panel.

Scoring on an 11-point numerical rating scale for the strength of recommendation was done by email by each expert for each bullet point after the meeting.

The methodology and detailed results of the SLR are described elsewhere in two separate papers: one dealing with biological agents and the other with all other management aspects such as non-biological drugs, education and physiotherapy (submitted).

RESULTS

General definitions

The target population was defined as follows: the recommendations were to apply to all patients fulfilling the modified New York criteria for AS, independent of extra-articular manifestations. Patients of all ages, including paediatric patients, were included, and all pharmacological and non-pharmacological interventions for AS were taken into account.

The first discussion addressed whether the terminology of the recommendations should be changed to 'Recommendations for the management of axial spondyloarthritis'. The arguments in favour were mainly that the new classification criteria for axial spondyloarthritis^{25 26} are now available and they should therefore be included in the recommendations. The arguments against this were rather pragmatic, such as 'the world of rheumatology is not yet ready for that change'. Furthermore, there is a paucity of papers in early disease. The group finally decided to stick to the term 'AS' for the time being. However, every expert expressed the opinion that patients with early axial spondyloarthritis who do not yet fulfil the modified New York criteria are part of the same spectrum of disease and that these management recommendations most likely apply equally to those patients. Importantly, this patient population is already well recognised in the last update of the ASAS recommendations for anti-TNF therapy.¹⁵ However, it should also be clearly stated that not all patients who fulfil classification criteria for axial spondyloarthritis will necessarily develop structural damage with radiographic changes in the sacroiliac joints and/or spine, which is presently considered essential in order for patients to fulfil currently used criteria for AS.^{29 30} This is actually similar to patients fulfilling the 2010 criteria for rheumatoid arthritis (RA) versus patients fulfilling the 1987 criteria for RA.

Although there are first hints that TNF blockers may be safer in AS compared with RA,³¹ a decision was made not to create a unique update on the safety of biological agents in AS/spondyloarthritis, but rather to rely on the extensive work done by Furst *et al*³² who have undertaken an annual consensus document on this topic from the 'Targeted therapies' meeting.

Results of the SLR

The detailed results will be published elsewhere (submitted). However, the information that was obtained from the SLR was taken into account during the discussions of each bullet point.

Results of the discussions

The first change the expert group agreed on was, by analogy with other EULAR recommendations (eg, management recommendations for RA, 6), to define overarching principles of management.

Bullet point number 3 in the first published version of the recommendations¹ stating that the optimal management of patients with AS requires a combination of non-pharmacological and pharmacological treatment modalities has now been moved to this section.

Of note, the citations in this section are not the complete results of the SLR and they are not complete. They are just examples given to document the basis of the statements and notations made in the text.

An overview of the new recommendation is given in box 1. The overarching principles of the management of patients with AS are:

- ▶ AS is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary treatment coordinated by the rheumatologist.
- ▶ The primary goal of treating the patient with AS is to maximise long term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation.
- ▶ Treatment of AS should aim at optimal care and must be based on a shared decision between the patient and the rheumatologist.
- ▶ The optimal management of patients with AS requires a combination of non-pharmacological and pharmacological treatment modalities.

Comment

Patients with AS present with different disease manifestations²⁴ and a high proportion may run a severe course of disease.³³ The main health problems of patients with AS have recently been listed as part of an International Classification of Functioning, Disability and Health consensus process.^{34 35}

It is important to stress that the rheumatologist is the expert who should take the lead in the management of patients with AS. The major aim for the treatment of rheumatic diseases is the preservation and gain of short and long-term health-related quality of life. The general view is that this is best achieved through control of symptoms and inflammation—with the aim to prevent deformity and disability due to structural damage caused by new bone formation and the decline of function and social participation.

Strength of recommendation: 9.5±0.1.

Thereafter, the bullet points were discussed point by point in considerable detail, and agreement was achieved on 11 points.

The updated recommendations are:

General treatment

The treatment of patients with AS should be individualised according to:

- ▶ The current manifestations of the disease (axial, peripheral, enthesal, extra-articular symptoms and signs)

Box 1 First update of the ASAS/EULAR recommendations for the management of AS

The overarching principles of the management of patients with AS are:

- ▶ AS is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary treatment coordinated by the rheumatologist.
- ▶ The primary goal of treating the patient with AS is to maximise long term health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation.
- ▶ Treatment of AS should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
- ▶ The optimal management of patients with AS requires a combination of non-pharmacological and pharmacological treatment modalities.

1. General treatment

The treatment of patients with AS should be tailored according to:

- ▶ The current manifestations of the disease (axial, peripheral, enthesal, extra-articular symptoms and signs).
- ▶ The level of current symptoms, clinical findings, and prognostic indicators.
- ▶ The general clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors).

2. Disease monitoring

The disease monitoring of patients with AS should include:

- ▶ Patient history (eg, questionnaires)
- ▶ Clinical parameters
- ▶ Laboratory tests
- ▶ Imaging
 - ▷ All according to the clinical presentation as well as the ASAS core set

The frequency of monitoring should be decided on an individual basis depending on:

- ▶ Course of symptoms
- ▶ Severity
- ▶ Treatment

3. Non-pharmacological treatment

- ▶ The cornerstone of non-pharmacological treatment of patients with AS is patient education and regular exercise.
- ▶ Home exercises are effective. Physical therapy with supervised exercises, land or water based, individually or in a group, should be preferred as these are more effective than home exercises.
- ▶ Patient associations and self-help groups may be useful.

4. Extra-articular manifestations and comorbidities

- ▶ The frequently observed extra-articular manifestations, for example, psoriasis, uveitis and IBD, should be managed in collaboration with the respective specialists.
- ▶ Rheumatologists should be aware of the increased risk of cardiovascular disease and osteoporosis.

5. Non-steroidal anti-inflammatory drugs

- ▶ NSAID, including Coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness.
- ▶ Continuous treatment with NSAID is preferred for patients with persistently active, symptomatic disease.
- ▶ Cardiovascular, gastrointestinal and renal risks should be taken into account when prescribing NSAID.

6. Analgesics

- ▶ Analgesics, such as paracetamol and opioid (like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.

7. Glucocorticoids

- ▶ Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered.
- ▶ The use of systemic glucocorticoids for axial disease is not supported by evidence.

8. Disease-modifying antirheumatic drugs

- ▶ There is no evidence for the efficacy of DMARD, including sulfasalazine and methotrexate, for the treatment of axial disease.
- ▶ Sulfasalazine may be considered in patients with peripheral arthritis.

9. Anti-TNF therapy

- ▶ Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations.
- ▶ There is no evidence to support the obligatory use of DMARD before or concomitant with anti-TNF therapy in patients with axial disease.
- ▶ There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular/enthesal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account.
- ▶ Switching to a second TNF blocker might be beneficial especially in patients with loss of response.
- ▶ There is no evidence to support the use of biological agents other than TNF inhibitors in AS.

10. Surgery

- ▶ Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age.
- ▶ Spinal corrective osteotomy may be considered in patients with severe disabling deformity.
- ▶ In patients with AS and an acute vertebral fracture a spinal surgeon should be consulted.

11. Changes in the disease course

- ▶ If a significant change in the course of the disease occurs, other causes than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

- ▶ The level of current symptoms, clinical findings and prognostic indicators
- ▶ The general clinical status (age, gender, comorbidities, concomitant medications, psychosocial factors).

Comment

This general bullet point was not changed. It stresses that there may be considerable variation in how AS patients may present to the rheumatologist. The aim of management and appropriate interventions may thus also differ substantially. This implies that these aims must be tailored to the unique features of the particular AS patient.

Strength of recommendation: 9.5±0.1.

Disease monitoring

The disease monitoring of patients with AS should include:

- ▶ Patient history (eg, questionnaires)
- ▶ Clinical parameters
- ▶ Laboratory tests
- ▶ Imaging
 - ▷ All according to the clinical presentation as well as the ASAS core set.

The frequency of monitoring should be decided on an individual basis depending on:

- ▶ Course of symptoms
- ▶ Severity
- ▶ Treatment.

Comment

This bullet point was not changed. It basically leaves the decision as to how frequently patients should be monitored to the rheumatologist in charge of management. This is mainly due to the fact that the course of disease may differ substantially between patients and different aspects, as stated in the bullet point, may need to be considered.

Importantly, experts agreed that, in general, spinal x-rays should not be repeated more frequently than every 2 years unless clearly indicated in individual cases. This recommendation is based on the experience from clinical studies.^{36 37}

Strength of recommendation: 9.4±0.2.

Non-pharmacological treatment

- ▶ The cornerstone of non-pharmacological treatment of patients with AS is patient education and regular exercise.
- ▶ Home exercises are effective. Physical therapy with supervised exercises, land or water based, individually or in a group, should be preferred as these are more effective than home exercises.
- ▶ Patient associations and self-help groups may be useful.

For comparison, the old recommendation was: non-pharmacological treatment of AS should include patient education and regular exercise. Individual and group physical therapy should be considered. Patient associations and self-help groups may be useful.

Comment

This bullet point was changed according to the SLR and the recent Cochrane review on the subject,³⁸ and was supported by the view of an experienced physiotherapist (HD) and the participating patients.

Strength of recommendation: 8.8±0.4.

Extra-articular manifestations and comorbidities

- ▶ The frequently observed extra-articular manifestations, eg, psoriasis, uveitis, and chronic inflammatory bowel disease

(IBD), should be managed in collaboration with the respective specialists.

- ▶ Rheumatologists should be aware of an increased risk of cardiovascular disease and osteoporosis.

Comment

This is a new bullet point, with agreement being achieved after considerable discussion. The main argument was that extra-articular manifestations are rather frequent in AS and the entire spectrum of spondyloarthritis,³⁹ and that they constitute a frequent challenge in management that clearly requires cooperation between specialties.

On the other hand, there are frequent comorbidities that require the attention of the managing rheumatologist. These include low bone mineral density, osteoporotic fractures^{40 41} and cardiovascular diseases,^{42 43} which have been reported to occur in AS and spondyloarthritis at an increased rate compared with the general population.

The rheumatologist is encouraged to identify patients at risk and the potential additional risk factors. At this time, it is difficult to make a clear-cut recommendation on the management of osteopaenia and osteoporosis for patients with AS in the absence of any studies on the subject.

Regarding the management of cardiovascular risk there are recent EULAR recommendations that propose an annual risk assessment related to national guidelines.⁴⁴ Although this is mainly intended for patients with RA, these same guidelines should also be considered for patients with AS and psoriatic arthritis. Rheumatologists are referred to local guidelines for the management of cardiovascular risk and, if no local guidelines are available, the management should be carried out according to the systematic coronary risk evaluation (SCORE) function⁴⁵ (for overview see Cooney *et al*).⁴⁶ In addition to appropriate cardiovascular risk management, aggressive suppression of the inflammatory process is recommended to lower the cardiovascular risk further.

Strength of recommendation: 9.0±0.3.

Non-steroidal anti-inflammatory drugs

- ▶ Non-steroidal anti-inflammatory drugs (NSAID), including Coxibs, are recommended as first-line drug treatment for AS patients with pain and stiffness.
- ▶ Continuous treatment with NSAID is preferred for patients with persistently active, symptomatic disease.
- ▶ Cardiovascular, gastrointestinal and renal risks should be taken into account when prescribing NSAID.

For comparison, the old recommendation was: NSAID are recommended as first-line drug treatment for patients with AS with pain and stiffness. In those with increased gastrointestinal risk, non-selective NSAID plus a gastroprotective agent, or a selective COX-2 inhibitor with or without a gastroprotective agent could be used.

Comment

This bullet point was subject to some minor modifications but the significance of the statement remains unchanged.

The main issues are still that NSAID are recommended as the first-line drug therapy, that NSAID are recommended to be taken continuously in active patients, and that NSAID are considered relatively safe in the population of patients with AS, although the cardiovascular, gastrointestinal and renal risks may be somewhat increased in this population.

The main challenges are that it is unclear whether a cut-off such as a Bath ankylosing spondylitis disease activity index of 4 is valuable in classifying patients as responders or non-responders with regard to NSAID therapy, whether NSAID

should be taken continuously regardless of symptoms by all (even asymptomatic) patients to prevent new bone formation, whether long-term NSAID therapy is safe, whether patients at risk can be readily identified, and how this should be done in clinical practice.

There is evidence that NSAID are efficacious for the relief of pain and stiffness in patients with AS⁴⁷ for both short-term and prolonged periods of treatment.^{48, 49} The efficacy is, at least partly, dose related.⁴⁸ There seems to be no effect on spinal inflammation as assessed by MRI in one small study,⁵⁰ but continuous therapy may be superior in the prevention of new bone formation.⁵¹ Coxibs may be safe for short-term therapy even in patients with IBD.⁵² One recent step forward for clinical trials in AS has been the ASAS proposal on how information on NSAID intake should be collected in studies.⁵³

Strength of recommendation: 9.3±0.3.

Analgesics

- ▶ Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.

Comment

This bullet point has remained unchanged. This topic has been the source of frequent discussion and there are experts who have proposed eliminating this bullet point, but the majority still felt that inclusion of this bullet point was necessary because it was important to draw attention to the possibility that not all back pain in AS may derive from spinal inflammation.

Strength of recommendation: 8.0±0.5.

Glucocorticoids

- ▶ Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered.
- ▶ The use of systemic glucocorticoids for axial disease is not supported by evidence.

Comment

This bullet point has remained unchanged. There have been no new studies and the available literature is still scarce.

Strength of recommendation: 8.9±0.4.

Disease modifying antirheumatic drugs

- ▶ There is no evidence for the efficacy of disease-modifying antirheumatic drugs (DMARD), including sulfasalazine and methotrexate, for the treatment of axial disease.
- ▶ Sulfasalazine may be considered in patients with peripheral arthritis.

Comment

This bullet point has remained unchanged. After the last Cochrane review⁵⁴ there were two new studies on sulfasalazine,^{55, 56} but the experts did not find that these provided sufficient new information to change this bullet point. The results of the first study, which was performed mainly in patients who had early spondyloarthritis, are conflicting,⁵⁵ whereas in the head-to-head trial against etanercept there was no placebo group.⁵⁶ Overall, a marginal positive effect of sulfasalazine with a rather limited effect size in AS cannot be excluded. Therefore, no strong recommendation can be given to support its use but the rheumatologist may decide on a trial of sulfasalazine for a limited period, usually not more than 4 months, after which further benefit is unlikely. The majority

of the studies suggest some efficacy of sulfasalazine in patients with peripheral spondyloarthritis and in the prevention of anterior uveitis. However, etanercept was more efficacious in the active comparator trial.⁵⁶ Finally, there is clearly no reason other than economic to recommend the obligatory use of a conventional DMARD in AS before anti-TNF therapy.

The data on methotrexate are still very limited and no positive recommendation can be given on an evidence basis. After the last Cochrane review⁵⁷ there was one new open-label study with a high dose of methotrexate given subcutaneously,⁵⁸ which again demonstrated no effect on patients with axial disease.

Most rheumatologists will try methotrexate in patients with predominant peripheral spondyloarthritis, but no evidence-based recommendation can presently support this.

Strength of recommendation: 9.4±0.2.

Anti-TNF therapy

- ▶ Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations.
- ▶ There is no evidence to support the obligatory use of DMARD before or concomitant with anti-TNF therapy in patients with axial disease.
- ▶ There is no evidence to support a difference in efficacy of the various TNF inhibitors on the axial and articular/enthesal disease manifestations; but in the presence of IBD a difference in gastrointestinal efficacy needs to be taken into account.
- ▶ Switching to a second TNF blocker might be beneficial especially in patients with loss of response.
- ▶ There is no evidence to support the use of biological agents other than TNF inhibitors in AS.

For comparison, the old recommendation was: anti-TNF treatment should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations. There is no evidence to support the obligatory use of DMARD before, or concomitant with, anti-TNF treatment in patients with axial disease.

Comment

This recommendation was substantially changed—based on extensive discussions related to the literature review, as the vast majority of new studies published in the past 5 years were related to anti-TNF therapy. The statement is of course strongly related to the recent update of the ASAS recommendations on anti-TNF therapy in AS.¹⁵

Since the last systematic review¹¹ there were many new studies. In addition to infliximab and etanercept, adalimumab⁵⁹ and golimumab⁶⁰ have also been approved. There are substantial data on patient-reported outcomes.⁶¹ There is evidence that patients with advanced disease⁶² also have some benefit, but patients with early⁶³ and very early⁶⁴ disease seem to have even more benefit. The highest remission rate reported is up to 50% after 16 weeks⁶⁴ in patients with inflammatory back pain⁶⁵ of less than 3 years (mean 15 months) and sacroiliitis on MRI but not on radiographs. Of note, the majority of the patients in these trials did not fulfil the modified New York criteria for AS.

The retention rate of patients with AS after 1 year of anti-TNF therapy was better than for patients with RA in a large registry.⁶⁶ There is evidence that the efficacy of anti-TNF therapy lasts over several years.^{67–69}

Spinal inflammation, as assessed by MRI, improves substantially after anti-TNF therapy.⁷⁰ Radiographic progression (mainly

new bone formation) does not seem to be inhibited by anti-TNF therapy,⁷¹ but there is also no evidence that syndesmophyte formation is accelerated.

The major new aspect of the updated recommendations is the differential effect of anti-TNF therapy when available drugs have similar efficacy on musculoskeletal manifestations but differential efficacy in clinically symptomatic IBD.⁷² Here the monoclonal antibodies work better than the fusion protein (infliximab is approved for both Crohn's disease (CD) and ulcerative colitis, adalimumab for CD, no data yet available for golimumab). The differences regarding acute anterior uveitis are less evident.⁷³ The presence or absence of psoriasis does not seem to make a difference as regards efficacy on musculoskeletal symptoms.⁷⁴

There is evidence that anti-TNF agents improve the signs and symptoms of peripheral arthritis and enthesitis.^{75 76}

Furthermore, a recommendation for switching is included for the first time since several studies have suggested high success rates.^{77–79} It was discussed that antibody formation^{80 81} may be involved in the phenomenon of loss of response (secondary non-response) and that such patients seem to have an even higher potential for response to a second TNF blocker than primary non-responders.

The statement that there is no evidence for the efficacy of other biological therapies in AS is also new. It is based on two studies evaluating rituximab and abatacept, which both failed to show convincing response rates in patients who had failed TNF blockers.^{82 83} The response rate to rituximab in TNF-naive AS patients deserves further study.⁸²

Some experts stressed the importance of exercise and regular physiotherapy in patients with AS under treatment with TNF blockers, but the literature on this topic is still scarce.⁸⁴

Strength of recommendation: 9.4±0.2.

Surgery

- ▶ Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age.
- ▶ Spinal corrective osteotomy may be considered in patients with severe disabling deformity.
- ▶ In patients with AS and an acute vertebral fracture a spinal surgeon should be consulted.

For comparison, the old recommendation was: total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal surgery, such as corrective osteotomy and stabilisation procedures, may be of value in selected patients.

Comment

This bullet point was modified based on discussions with the two orthopaedic surgeons in the expert committee. The significance of hip involvement has been confirmed by a recent multinational study.^{85 86} A statement related to that problem therefore remains important, and the first sentence on total hip arthroplasty remains unchanged. Cement is only rarely used in young patients,⁸⁷ and heterotopic ossification does not seem to be a problem in patients with AS.⁸⁸ The recommendation on spinal surgery was intensively discussed and a more detailed statement agreed on.

The second statement addresses an elective surgical procedure in the spine, which was shown to be beneficial for many patients with advanced AS and hyperkyphosis who have lost their horizontal vision ability. This technically challenging operation, which is only performed in experienced centres

and is not available in some countries, leads to at least the partial correction of kyphosis. Triangular pieces of bone are removed from selected vertebral bodies (pedicle subtraction osteotomy) before the spine is re-stabilised by metallic bars and screws.

The third statement addresses spinal fractures that may lead to instability of the spine. These are often but not always rather acute clinical situations, which may or may not be associated with neurological symptoms.^{89–94} In addition, as mechanical stress may prevent discovertebral spinal lesions from fusion and lead to the development of pseudarthrosis, a spinal surgeon should at least be consulted in patients with symptomatic discovertebral lesions.⁹⁵

This has been regarded as so important that an extra bullet point, no 11, was added.

Strength of recommendation: 9.2±0.3.

Changes in the disease course

- ▶ If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

Comment

This is a new recommendation. The major point is that changes in the course of the disease should be carefully evaluated and MRI performed—especially in situations in which the nature of back pain changes. An experienced spinal surgeon may need to be consulted. It seems important to stress that not all AS patients with spinal fractures have neurological symptoms (and not all need to be operated on).

There are other important differential diagnoses such as spinal infections.

Strength of recommendation: 9.0±0.3.

DISCUSSION

The ASAS/EULAR recommendations were successfully updated. The introduction of overarching principles led to some changes, eg, one bullet point and one sentence was moved to this section. There are now 11 bullet points including two new points: one for extra-articular manifestations and one for changes in the clinical course of AS.

A patient version of the recommendations will be developed. We encourage translation of these recommendations into various languages in a collaboration between rheumatologists and patients. After presentation at the EULAR 2010 meeting in Rome and publication in the EULAR journal, individual countries can now take on dissemination.

The collaboration between ASAS and EULAR has again been very successful and should be continued for the next update that may be renamed according to the new classification criteria for axial spondyloarthritis. There will be a need for further discussion as to whether the new criteria for peripheral spondyloarthritis⁹⁶ should give rise to separate recommendations for these patients.

Although it was decided that these recommendations concentrate on AS, the authors are well aware that the treatment of patients with non-radiographic axial spondyloarthritis is also a very important topic. There are now data of clinical trials available that address this question in a controlled manner.^{63 64} They provide evidence that anti-TNF agents work in early disease in at least the same but probably in an even superior way.

The original publication has already set a standard for the management of patients with AS. As we feel that this update has even improved the original set we are confident that these recommendations will be useful for patients and healthcare workers, including rheumatologists and other physicians treating patients with AS, as well as physiotherapists.

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Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Zochling J**, van der Heijde D, Burgos-Vargas R, *et al*. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006;**65**:442–52.
2. **Zhang W**, Doherty M, Bardin T, *et al*.; for the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCIIT). *Ann Rheum Dis* 2006;**65**:1312–24.
3. **Mukhtyar C**, Guillevin L, Cid MC, *et al*.; for the European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009;**68**:310–17.
4. **Landewé RB**, Günther K, Lukas C, *et al*. EULAR/EFORT recommendations for the diagnosis and initial management of patients with acute or recent onset swelling of the knee. *Ann Rheum Dis* 2010;**69**:12–19.
5. **Kowal-Bielecka O**, Landewé R, Avouac J, *et al*.; EUSTAR Co-Authors. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis* 2009;**68**:620–8.
6. **Smolen JS**, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;**69**:964–75.
7. **Dougados M**, Betteridge N, Burmester GR, *et al*. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;**63**:1172–6.
8. The AGREE Collaboration. Appraisal and Guidelines for Research and Evaluation (AGREE) Instrument, 2001. www.agreecollaboration.org (accessed Feb 2010).
9. **Moher D**, Tetzlaff J, Tricco AC, *et al*. Epidemiology and reporting characteristics of systematic reviews. *PLoS Med* 2007;**4**:e78.

10. **Shojania KG**, Sampson M, Ansari MT, *et al*. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med* 2007;**147**:224–33.
11. **Zochling J**, van der Heijde D, Dougados M, *et al*. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. *Ann Rheum Dis* 2006;**65**:423–32.
12. **van der Heijde D**, Bellamy N, Calin A, *et al*. Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group. *J Rheumatol* 1997;**24**:2225–9.
13. **Braun J**, Pham T, Sieper J, *et al*.; ASAS Working Group. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003;**62**:817–24.
14. **Braun J**, Davis J, Dougados M, *et al*. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006;**65**:316–20.
15. **van der Heijde D**, Sieper J, Maksymowych WP, *et al*. (Second) Update of the ASAS recommendations on the use of TNF-blockers in ankylosing spondylitis [abstract]. *Arthritis and Rheumatism* 2009;**60**(Suppl 10):1790.
16. **Hewlett SA**. Patients and clinicians have different perspectives on outcomes in arthritis. *J Rheumatol* 2003;**30**:877–9.
17. **Kiltz U**, van der Heijde D, Mielants H, *et al*. ASAS/EULAR recommendations for the management of ankylosing spondylitis: the patient version. *Ann Rheum Dis* 2009;**68**:1381–6.
18. **Gossec L**, Dougados M, Phillips C, *et al*. Dissemination and evaluation of the ASAS/EULAR recommendations for the management of ankylosing spondylitis: results of a study among 1507 rheumatologists. *Ann Rheum Dis* 2008;**67**:782–8.
19. **Braun J**, Sieper J. [Dissemination and evaluation of ASAS/EULAR recommendations for the management of ankylosing spondylitis in Europe]. *Z Rheumatol* 2009;**68**:417–19.
20. **Braun J**, Zochling J, Märker-Hermann E, *et al*. [Recommendations for the management of ankylosing spondylitis after ASAS/EULAR. Evaluation in the German language area]. *Z Rheumatol* 2006;**65**:728–42.
21. **Burgos-Vargas R**, Abud-Mendoza C, Díaz-Jouanen E, *et al*. [Treatment guidelines for ankylosing spondylitis and its effect on Mexican rheumatology]. *Gac Med Mex* 2009;**145**:41–9.
22. **Kiltz U**, Feldtkeller E, Braun J. [Patient evaluation of the German version of the ASAS/EULAR recommendations for the management of ankylosing spondylitis]. *Z Rheumatol* 2008;**67**:694–700; 702.
23. **Kiltz U**, Feldtkeller E, Braun J. German patient version of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Z Rheumatol* 2010;**69**:171–4; 176–9.
24. **Braun J**, Sieper J. Ankylosing spondylitis. *Lancet* 2007;**369**:1379–90.
25. **Rudwaleit M**, Landewé R, van der Heijde D, *et al*. The development of assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;**68**:770–6.
26. **Rudwaleit M**, van der Heijde D, Landewé R, *et al*. The development of assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;**68**:777–83.
27. **Rudwaleit M**, Jurik AG, Hermann KG, *et al*. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI Group. *Ann Rheum Dis* 2009;**68**:1520–7.
28. **Sieper J**, Rudwaleit M, Baraliakos X, *et al*. The assessment of spondyloarthritis international society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;**68**(Suppl 2):ii1–44.
29. **Sampaio-Barros PD**, Bortoluzzo AB, Conde RA, *et al*. Undifferentiated spondyloarthritis: a longterm followup. *J Rheumatol* 2010;**37**:1195–9.
30. **Bennett AN**, McGonagle D, O'Connor P, *et al*. Severity of baseline magnetic resonance imaging—evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis and Rheumatism* 2008;**58**:3413–18.
31. **Fouque-Aubert A**, Jette-Paulin L, Combescore C, *et al*. Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. *Ann Rheum Dis* 2010;**69**:1756–61.
32. **Furst DE**, Keystone EC, Fleischmann R, *et al*. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2009. *Ann Rheum Dis* 2010;**69**(Suppl 1):i2–29.
33. **Zink A**, Braun J, Listing J, *et al*. Disability and handicap in rheumatoid arthritis and ankylosing spondylitis—results from the German rheumatological database. German Collaborative Arthritis Centers. *J Rheumatol* 2000;**27**:613–22.
34. WHO. International classification of functioning, disability and health. Geneva: World Health Organization, 2001.
35. **Boonen A**, Braun J, van der Horst-Bruinsma IE, *et al*. The ASAS/WHO ICF core sets for ankylosing spondylitis: how to classify the impact of AS on functioning and health. *Ann Rheum Dis* 2010;**69**:102–7.

36. **Spoorenberg A**, de Vlam K, van der Linden S, *et al.* Radiological scoring methods in ankylosing spondylitis. Reliability and change over 1 and 2 years. *J Rheumatol* 2004;**31**:125–32.
37. **van der Heijde D**, Landewé R, van der Linden S. How should treatment effect on spinal radiographic progression in patients with ankylosing spondylitis be measured? *Arthritis and Rheumatism* 2005;**52**:1979–85.
38. **Dagfinrud H**, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. *Cochrane Database Syst Rev* 2008;**1**:CD002822.
39. **Vander Cruyssen B**, Ribbens C, Boonen A, *et al.* The epidemiology of ankylosing spondylitis and the commencement of anti-TNF therapy in daily rheumatology practice. *Ann Rheum Dis* 2007;**66**:1072–7.
40. **Karberg K**, Zochling J, Sieper J, *et al.* Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *J Rheumatol* 2005;**32**:1290–8.
41. **Vosse D**, Landewé R, van der Heijde D, *et al.* Ankylosing spondylitis and the risk of fracture: results from a large primary care-based nested case–control study. *Ann Rheum Dis* 2009;**68**:1839–42.
42. **Peters MJ**, Visman I, Nielen MM, *et al.* Ankylosing spondylitis: a risk factor for myocardial infarction? *Ann Rheum Dis* 2010;**69**:579–81.
43. **Peters MJ**, van Eijk IC, Smulders YM, *et al.* Signs of accelerated preclinical atherosclerosis in patients with ankylosing spondylitis. *J Rheumatol* 2010;**37**:161–6.
44. **Peters MJ**, Symmons DP, McCarey D, *et al.* EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;**69**:325–31.
45. **Conroy RM**, Pyörälä K, Fitzgerald AP, *et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
46. **Cooney MT**, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. *J Am Coll Cardiol* 2009;**54**:1209–27.
47. **Escalac C**, Trijau S, Dougados M. Evaluation of the treatment effect of NSAIDs/TNF blockers according to different domains in ankylosing spondylitis: results of a meta-analysis. *Rheumatology (Oxford)* 2010;**49**:1317–25.
48. **van der Heijde D**, Baraf HS, Ramos-Remus C, *et al.* Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis and Rheumatism* 2005;**52**:1205–15.
49. **Sieper J**, Klopsch T, Richter M, *et al.* Comparison of two different dosages of celecoxib with diclofenac for the treatment of active ankylosing spondylitis: results of a 12-week randomised, double-blind, controlled study. *Ann Rheum Dis* 2008;**67**:323–9.
50. **Jarrett SJ**, Sivera F, Cawkwell LS, *et al.* MRI and clinical findings in patients with ankylosing spondylitis eligible for anti-tumour necrosis factor therapy after a short course of etoricoxib. *Ann Rheum Dis* 2009;**68**:1466–9.
51. **Wanders A**, Heijde D, Landewé R, *et al.* Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis and Rheumatism* 2005;**52**:1756–65.
52. **El Miedany Y**, Youssef S, Ahmed I, *et al.* The gastrointestinal safety and effect on disease activity of etoricoxib, a selective cox-2 inhibitor in inflammatory bowel diseases. *Am J Gastroenterol* 2006;**101**:311–17.
53. **Dougados M**, Simon P, Braun J, *et al.* ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. *Ann Rheum Dis* 2011;**70**:249–51.
54. **Chen J**, Liu C. Sulfasalazine for ankylosing spondylitis. *Cochrane Database Syst Rev* 2005;**2**:CD004800.
55. **Braun J**, Zochling J, Baraliakos X, *et al.* Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. *Ann Rheum Dis* 2006;**65**:1147–53.
56. **Braun J**, van der Horst-Bruinsma IE, Huang F, *et al.* Clinical efficacy and safety of etanercept versus sulfasalazine in ankylosing spondylitis patients: a randomized, double-blind study (ASCEND Trial). *Arthritis and Rheumatism*. Published Online First: 10 January 2011. doi:10.1002/art.30223.
57. **Chen J**, Liu C, Lin J. Methotrexate for ankylosing spondylitis. *Cochrane Database Syst Rev* 2006;**4**:CD004524.
58. **Haibel H**, Brandt HC, Song IH, *et al.* No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. *Ann Rheum Dis* 2007;**66**:419–21.
59. **van der Heijde D**, Kivitz A, Schiff MH, *et al.*; ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis and Rheumatism* 2006;**54**:2136–46.
60. **Inman RD**, Davis JC Jr, Heijde D, *et al.* Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. *Arthritis and Rheumatism* 2008;**58**:3402–12.
61. **Braun J**, McHugh N, Singh A, *et al.* Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. *Rheumatology (Oxford)* 2007;**46**:999–1004.
62. **van der Heijde D**, Pangan AL, Schiff MH, *et al.*; ATLAS Study Group. Adalimumab effectively reduces the signs and symptoms of active ankylosing spondylitis in patients with total spinal ankylosis. *Ann Rheum Dis* 2008;**67**:1218–21.
63. **Haibel H**, Rudwaleit M, Listing J, *et al.* Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis and Rheumatism* 2008;**58**:1981–91.
64. **Barkham N**, Keen HI, Coates LC, *et al.* Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis and Rheumatism* 2009;**60**:946–54.
65. **Braun J**, Inman R. Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis. *Ann Rheum Dis* 2010;**69**:1264–8.
66. **Heiberg MS**, Koldingsnes W, Mikkelsen K, *et al.* The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis and Rheumatism* 2008;**59**:234–40.
67. **van der Heijde D**, Schiff MH, Sieper J, *et al.*; ATLAS Study Group. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. *Ann Rheum Dis* 2009;**68**:922–9.
68. **Davis JC Jr**, van der Heijde DM, Braun J, *et al.* Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis* 2008;**67**:346–52.
69. **Braun J**, Baraliakos X, Listing J, *et al.* Persistent clinical efficacy and safety of anti-tumour necrosis factor alpha therapy with infliximab in patients with ankylosing spondylitis over 5 years: evidence for different types of response. *Ann Rheum Dis* 2008;**67**:340–5.
70. **Braun J**, Landewé R, Hermann KG, *et al.*; ASSERT Study Group. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. *Arthritis and Rheumatism* 2006;**54**:1646–52.
71. **van der Heijde D**, Landewé R, Einstein S, *et al.* Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis and Rheumatism* 2008;**58**:1324–31.
72. **Braun J**, Baraliakos X, Listing J, *et al.* Differences in the incidence of flares or new onset of inflammatory bowel diseases in patients with ankylosing spondylitis exposed to therapy with anti-tumor necrosis factor alpha agents. *Arthritis and Rheumatism* 2007;**57**:639–47.
73. **Braun J**, Baraliakos X, Listing J, *et al.* Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis and Rheumatism* 2005;**52**:2447–51.
74. **Braun J**, Rudwaleit M, Kary S, *et al.* Clinical manifestations and responsiveness to adalimumab are similar in patients with ankylosing spondylitis with and without concomitant psoriasis. *Rheumatology (Oxford)* 2010;**49**:1578–89.
75. **Rudwaleit M**, Van den Bosch F, Kron M, *et al.* Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. *Arthritis Res Ther* 2010;**12**:R117.
76. **Dougados M**, Combe B, Braun J, *et al.* A randomised, multicentre, double-blind, placebo-controlled trial of etanercept in adults with refractory heel enthesitis in spondyloarthritis: the HEEL trial. *Ann Rheum Dis* 2010;**69**:1430–5.
77. **Cantini F**, Niccoli L, Benucci M, *et al.* Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. *Arthritis and Rheumatism* 2006;**55**:812–16.
78. **Coates LC**, Cawkwell LS, Ng NW, *et al.* Real life experience confirms sustained response to long-term biologics and switching in ankylosing spondylitis. *Rheumatology (Oxford)* 2008;**47**:897–900.
79. **Pradeep DJ**, Keat AC, Gaffney K, *et al.* Switching anti-TNF therapy in ankylosing spondylitis. *Rheumatology (Oxford)* 2008;**47**:1726–7.
80. **de Vries MK**, Wolbink GJ, Stapel SO, *et al.* Decreased clinical response to infliximab in ankylosing spondylitis is correlated with anti-infliximab formation. *Ann Rheum Dis* 2007;**66**:1252–4.
81. **de Vries MK**, Brouwer E, van der Horst-Bruinsma IE, *et al.* Decreased clinical response to adalimumab in ankylosing spondylitis is associated with antibody formation. *Ann Rheum Dis* 2009;**68**:1787–8.
82. **Song IH**, Heldmann F, Rudwaleit M, *et al.* Different response to rituximab in tumor necrosis factor blocker-naïve patients with active ankylosing spondylitis and in patients in whom tumor necrosis factor blockers have failed: a twenty-four-week clinical trial. *Arthritis and Rheumatism* 2010;**62**:1290–7.
83. **Song IH**, Heldmann H, Rudwaleit M, *et al.* Treatment of active ankylosing spondylitis with abatacept – an open label 24-week study. *Ann Rheum Dis* 2010;**69**(Suppl 3):60.
84. **Colina M**, Ciancio G, Garavini R, *et al.* Combination treatment with etanercept and an intensive spa rehabilitation program in active ankylosing spondylitis. *Int J Immunopathol Pharmacol* 2009;**22**:1125–9.
85. **Vander Cruyssen B**, Muñoz-Gomariz E, Font P, *et al.*; ASPECT-REGISPONSER-RESPONDIA working group. Hip involvement in ankylosing spondylitis: epidemiology and risk factors associated with hip replacement surgery. *Rheumatology (Oxford)* 2010;**49**:73–81.

86. **Baraliakos X**, Braun J. Hip involvement in ankylosing spondylitis: what is the verdict? *Rheumatology (Oxford)* 2010;**49**:3–4.
87. **Sochart DH**, Porter ML. Long-term results of total hip replacement in young patients who had ankylosing spondylitis. Eighteen to thirty-year results with survivorship analysis. *J Bone Joint Surg Am* 1997;**79**:1181–9.
88. **Bhan S**, Eachempati KK, Malhotra R. Primary cementless total hip arthroplasty for bony ankylosis in patients with ankylosing spondylitis. *J Arthroplasty* 2008;**23**:859–66.
89. **Sapkas G**, Kateros K, Papadakis SA, *et al*. Surgical outcome after spinal fractures in patients with ankylosing spondylitis. *BMC Musculoskelet Disord* 2009;**10**:96.
90. **Fordham S**, Lloyd G. Clinical management of injured patients with ankylosing spondylitis. *BMJ* 2009;**339**:b2568.
91. **Whang PG**, Goldberg G, Lawrence JP, *et al*. The management of spinal injuries in patients with ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis: a comparison of treatment methods and clinical outcomes. *J Spinal Disord Tech* 2009;**22**:77–85.
92. **Westerveld LA**, Verlaan JJ, Oner FC. Spinal fractures in patients with ankylosing spinal disorders: a systematic review of the literature on treatment, neurological status and complications. *Eur Spine J* 2009;**18**:145–56.
93. **van Royen BJ**, Scheerder FJ, Jansen E, *et al*. ASKyphoplan: a program for deformity planning in ankylosing spondylitis. *Eur Spine J* 2007;**16**:1445–9.
94. **Kiaer T**, Gehrchen M. Transpedicular closed wedge osteotomy in ankylosing spondylitis: results of surgical treatment and prospective outcome analysis. *Eur Spine J* 2010;**19**:57–64.
95. **Bron JL**, de Vries MK, Snieders MN, *et al*. Discovertebral (Andersson) lesions of the spine in ankylosing spondylitis revisited. *Clin Rheumatol* 2009;**28**:883–92.
96. **Rudwaleit M**, van der Heijde D, Landewé R, *et al*. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;**70**:25–31.