REPORT

Outcomes in ankylosing spondylitis: what makes the assessment of treatment effects in ankylosing spondylitis different?

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There are four major challenges in the assessment of outcomes in patients with ankylosing spondylitis (AS) that are particularly relevant to the evaluation of new therapies. Firstly, measures of symptoms and impairment in AS are not specific for inflammatory processes, they also capture mechanical symptoms and fixed limitations. The non-specific nature of these measures may cause them to be less responsive and therefore less useful in determining treatment efficacy. Secondly, acute phase reactants have limited value as measures of AS activity and other surrogate markers have not yet been established. Thirdly, the assessment of the disease modifying potential of new therapies is hampered by the slow rate of spinal fusion. Fourthly, work disability has not been studied as an endpoint in clinical trials in AS, despite the fact that work disability is an important outcome in patients with AS. Research into ways to overcome these challenges in outcome measurement will help identify useful therapies and define the range of outcomes that they influence.

Health outcomes include all the consequences of an illness on a person's life. These include impairments (alterations in normal body structure or function), measures of health status (symptoms and functioning), quality of life, costs of illness, and mortality^{1–2} (table 1). Measures of impairments and health status are the outcomes most often used as endpoints in clinical trials. In ankylosing spondylitis (AS), specific measures of impairment and health status have been recommended as a core set to be included as endpoints in clinical trials^{3–4} (table 1).

The types of outcome measures used in AS are similar to those used for other types of inflammatory arthritis. However, AS presents special challenges in operationalising these outcomes into endpoints for clinical trials. These include:

- non-specific nature of measures of symptoms and impairments
- limited ability of common laboratory measures of inflammation to corroborate patient reported health status or clinician observed impairments
- difficulty of testing disease modification due to the slow progression of spinal fusion
- diversity of work disability that complicates testing in clinical trials.

MEASURES OF ANKYLOSING SPONDYLITIS ACTIVITY

Symptoms and signs

AS activity is reflected in patient reported symptom severity, limitations in functioning due to pain, stiffness, muscle

spasm, or joint swelling, and signs on physical examination. Signs of AS activity include limited ease of movement due to pain and muscle spasm, local tenderness, and joint or tendon sheath swelling. In the absence of peripheral joint involvement, the assessment of AS activity can be difficult because substantial low back pain and stiffness can be present without notable local tenderness or spasm, and with little limitation in movement. Marked tenderness and spasm on physical examination tend to be specific markers of AS activity, but are likely not sensitive. Adding to the difficulty in using the physical examination to quantify AS activity is the lack of standardised measures of spinal tenderness or spasm, so that even when these signs are present, there is no accepted scheme to grade their severity. Proposals for measures such as the physician rated Spinal Pain Score need further study.⁵

Spinal and chest wall flexibility, tested using modified Schober's test, lateral lumbar flexion, chest expansion, neck flexion and rotation, and occiput to wall distance, have been used as surrogate measures of spinal pain and stiffness, on the premise that inflammation and spasm will cause restricted movement. Although limitations in these measures may be due to inflammation, limitations may also be a consequence of spinal or costovertebral fusion. In patients with early AS who do not have spinal fusion, one may be more certain that limitations in these measures represent AS activity. However, among patients with some degree of spinal fusion, the relative contribution of reversible AS activity and irreversible fusion to the limitations may be difficult to resolve. Attribution of limitations in these measures to AS activity should be done only after considering the stage of AS and any recent temporal changes in symptoms that might have occurred. The dual aetiologies of limitations of spinal mobility may explain the reduced sensitivity to change of these measures; the irreversible limitations captured by these measures are not able to change with treatment.^{6–9} Schober's test may also be limited by ceiling effects because it only measures forward flexion rather than flexion and extension.¹⁰

Given these problems, the assessment of AS activity has come to rely on patient reported measures of symptom severity. The symptoms most commonly assessed are those most often reported as problems by patients: pain, stiffness, and tiredness. The Bath AS Disease Activity Index (BASDAI) aggregates measures of these symptoms in a single score, and has been endorsed by the ASsessment of Ankylosing Spondylitis working group as the currently preferred patient reported measure of symptom severity.^{11–12} However, recent studies have reported that patients with mechanical low back pain have BASDAI scores similar to those of patients with AS.^{13–14} These findings suggest that, despite its name, the BASDAI is not specifically measuring inflammatory symptoms in patients with AS, but is likely also measuring mechanical symptoms and stiffness due to spinal fusion. This

Table 1 Categories of health outcomes

Category	Definition	Representative components	Ankylosing spondylitis core set measures
Impairment	Alteration of normal body structure or function	Signs on physical examination, laboratory tests, radiographs	Modified Schober test, chest expansion, occiput to wall distance, swollen joint count, enthesitis index, erythrocyte sedimentation rate, spinal radiographs
Health status	Symptom severity and degree of functional limitation	Pain, mood, physical function, work ability	Patient reported spinal pain, stiffness, fatigue, function scale, patient global assessment
Quality of life	Subjective appraisal of health status	Satisfaction with level of symptoms and functioning	
Costs	Monetary costs of obtaining care and costs of lost work productivity	Costs of medications, costs of visits to care providers, costs of hospitalisations, costs of work loss	
Mortality			

lack of specificity may also account for the finding that the distribution of BASDAI scores remains relatively stable with the duration of AS, even over 40 years, when mechanical symptoms would be expected to supervene.¹⁵ Although patient reported measures are validated measures of symptoms, the attribution of these symptoms solely to disease activity may not always be correct. As was the case for the physical examination, patient reported measures should be interpreted in the context of the duration of AS and the degree of spinal fusion present. These points also highlight the importance of the physician assessment in the evaluation of patients for treatment with tumor necrosis factor (TNF) antagonists, as BASDAI scores alone may provide a false positive assessment of AS activity in patients with long-standing AS.^{12 16}

Laboratory tests

The importance of some of the shortcomings of the physical examination and patient reported measures of AS activity could be lessened if laboratory tests were available that corroborated, in a reliable and valid way, the degree of AS activity that was present. Laboratory tests are most useful as surrogate markers of disease activity when the test:

- is abnormal in most patients with active AS
- changes in parallel with other measures of AS activity
- improves with known effective treatment
- is not influenced by processes other than AS activity.

Unfortunately, no laboratory tests have been found that satisfy these criteria for the majority of patients with AS.

The erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration have been the laboratory measures studied most often. Elevated levels of either test have been reported in fewer than half of patients with AS, and the degree of elevation in most patients is modest.¹⁷ In trials of tumor necrosis factor (TNF) antagonists, median values of the ESR at baseline have ranged from 25 mm/h to 34 mm/h, and median values of CRP from 1.2 mg/dL to 3.0 mg/dL.^{18–24} However, both measures have been found to be moderately sensitive to change in these trials. The extent to which peripheral arthritis, hip involvement or inflammatory bowel disease contributes to the modest associations of the ESR and CRP with AS activity is unclear. Studies have not

examined the performance of these measures separately in patients with purely axial AS, which could be argued is the setting in which a laboratory marker of AS activity would be most useful.

Several new laboratory measures have been studied as potential biomarkers in AS^{25–38} (box 1). Some have been tested as diagnostic markers, and for others it is not clear if the marker was intended as a measure of AS activity or of structural damage. It would be unusual for a single measure to be both a good diagnostic marker and a good evaluative marker. Good diagnostic markers should be abnormal even in patients with low disease activity, which is not desirable for a measure used to evaluate disease activity.³⁹ The selection of patients and the design of a study would differ substantially depending on the intended purpose of the biomarker.

In the search for new surrogate markers specifically intended to assess AS activity, consideration should be given to what the standard for comparison should be. As noted above, patient reported measures of symptom severity have limitations, but may be useful standards in carefully selected groups of patients. Physician global assessment may also be useful if the assessments are blinded to the laboratory results. Magnetic resonance imaging of the spine could be argued to be the most objective standard for comparison, but the expense and logistical difficulties of imaging limits its feasibility in the early phases of testing of surrogate markers. Markers which were promising in early studies that used clinical reference standards might be selected for testing in

Box 1: Laboratory tests recently studied as biomarkers in ankylosing spondylitis

- Serum matrix metalloproteinase-3
- Serum interleukin-6
- Serum vascular endothelial growth factor
- Serum cartilage glycoprotein-39
- Serum C2C neopeptide
- Serum aggrecan 846 epitope
- Urine pyridinoline and deoxypyridinoline
- Urine C-terminal telopeptide-1

later studies using magnetic resonance imaging as the standard. Longitudinal studies that demonstrated changes in the marker with flares of AS activity or decreases in the marker in response to effective treatment would provide the most convincing evidence of the value of a surrogate marker of AS activity.⁴⁰

ASSESSING DISEASE MODIFICATION

Demonstration that an intervention could retard structural damage in AS would represent a major advance. Improvement of an inflammatory spinal lesion detected by magnetic resonance imaging may suggest the potential for disease modification, but the relation between bone marrow oedema and subsequent bone fusion is unclear.^{23 24 26 41–44} The best evidence for disease modification would be slowing or stopping the progression of bone fusion. Options for assessing bone fusion include the sacroiliac joints and the spine. The sacroiliac joints are not the optimal joints to study because visualisation is difficult, and because fusion of these joints occurs early, limiting the pool of patients for study. In contrast, the spine is more readily visualised, is affected later in the course of AS, and provides a large anatomical range over which changes can occur. Fusion of the spine also has functional consequences, so demonstration of disease modification here would be more clinically relevant than it would be in the sacroiliac joints.

Several methods have been developed to quantify the degree of spinal fusion in AS. The two methods most commonly used are the Bath AS Radiology Index, which grades the lumbar and cervical spines globally, and the modified Stoke AS Spine Score, which details abnormalities at each lumbar and cervical disc space.^{45 46} However, spinal fusion progresses slowly in AS. Even the most sensitive radiographic scoring methods detect only small changes over two years.⁴⁷ This limitation complicates the testing of disease modification using a clinical trial design, which rarely have durations of two years or longer, and which would potentially assign patients with active AS to an inactive treatment for a prolonged period. Solutions to this problem include selecting a subgroup of patients who have rapid progression for testing, in whom treatment effects might be observed in a shorter time period, or using an observational study design with historical controls.⁴⁸ Other imaging modalities might also provide a measure that is more sensitive to change than plain x rays.

WORK DISABILITY AS A STUDY ENDPOINT

Work disability is an important outcome of AS because AS affects patients during their working years. Work disability accounts for 47–75% of the costs of AS to society, and is an

important component to be considered in cost-effectiveness analyses of treatments.^{49–51} However, work disability has not been studied as a clinical trial endpoint. One difficulty is that the relevant endpoints differ with the stage of employment (table 2). Among those who are stably employed, the number of sick days, change in work hours or type of work, or need for help at work, could be tested as endpoints in controlled trials. These events are infrequent in non-selected patients with AS, with only 12.5% reporting a decrease in work hours and less than 4% reporting more than 10 sick days over a six month period.⁵² However, these events would be expected to be more common among patients with active AS, who would more likely be enrolled in clinical trials, and would likely be feasible as trial endpoints.

Persons with threatened work disability would be individuals at high risk for job loss due to the activity of AS or their occupation. These patients could be identified by their expressed concerns about ability to work, use of prolonged sick leaves, or referral to vocational rehabilitation. Among these patients, the endpoint would be maintained employment. Although best tested in a controlled trial, this may not be feasible or ethical in patients with active AS. Observational cohort studies would be subject to bias against a treatment effect, because people with more active AS might be more likely not only to stop working but also to receive aggressive treatment.

Among those who are recently work disabled, the endpoint would be return to work. This event would not likely be captured in a controlled trial. A cohort design might be useful, because bias due to adverse selection for treatment would be less. In this situation, those who are treated aggressively might be expected to be less likely to return to work, so any evidence of an increase in employment would argue for the effectiveness of the treatment. Direct intervention would likely not be feasible in those with long-term work disability. Time series methods that examined changes in rates of permanent work disability at the population level might be the best approach to determine if the introduction of new treatments influenced the risk of long-term work disability.

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REFERENCES

1 Ward MM. Assessment of health outcomes. In: Harris ED Jr, ed. *Kelley's Textbook of Rheumatology*, 7th edn. Philadelphia: Elsevier Science, 2005:435–46.

2 World Health Organization. *ICF: International Classification of Functioning, Disability, and Health. Introduction*. Geneva: World Health Organization, 2001. Available at: www3.who.int/icf/icftemplate.cfm (accessed 5 December 2001).

3 van der Heijde D, van der Linden S, Bellamy N, Calin A, Dougados M, Khan MA. Which domains should be included in a core set for endpoints in ankylosing spondylitis? Introduction to the ankylosing spondylitis module of OMERACT IV. *J Rheumatol* 1999;**26**:945–7.

4 van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. Progress report of the ASAS Working Group. Assessment in Ankylosing Spondylitis. *J Rheumatol* 1999;**26**:951–4.

5 Rudawleit M, Hilgert E, Haibel H, Sieper J. Evaluation of a spinal pain score performed by the rheumatologist in ankylosing spondylitis [abstract]. European League Against Rheumatism Scientific Meeting, 12–15 June 2003, Lisbon, Portugal.

6 Heikkilä S, Viitanen JV, Kautiainen H, Kauppi M. Sensitivity to change of mobility tests: effect of short term intensive physiotherapy and exercise on spinal, hip, and shoulder measurements in spondyloarthritis. *J Rheumatol* 2000;**27**:1251–6.

7 Haywood KL, Garratt AM, Jordan K, Dziedzic K, Dawes PT. Spinal mobility in ankylosing spondylitis: reliability, validity, and responsiveness. *Rheumatology* 2004;**43**:750–7.

Table 2 Approaches to studying work disability as a clinical endpoint in ankylosing spondylitis		
Work status	Study design	Endpoint
Stably employed	Controlled trial	Number of sick days Change in work hours Change in type of work Need for help at work
Employed but with threatened work disability	Controlled trial Cohort study	Maintenance of employment
Recently work disabled	Cohort study	Return to work
Long-term work disabled	Time series	Secular trend in rates of permanent work disability

- 8 **Jauregui E**, Conner-Spady B, Russell AS, Maksymowych WP. Clinimetric evaluation of the Bath Ankylosing Spondylitis Metrology Index in a controlled trial of pamidronate therapy. *J Rheumatol* 2004;**31**:2422–8.
- 9 **Wanders AJ**, Gorman JD, Davis JC, Landewe RB, van der Heijde DM. Responsiveness and discriminative capacity of the Assessments in Ankylosing Spondylitis disease-controlling antirheumatic therapy core set and other outcome measures in a trial of etanercept in ankylosing spondylitis. *Arthritis Rheum* 2004;**51**:1–8.
- 10 **Ward MM**, Kuzis S. Ceiling effects and the Schober test. *J Rheumatol* 2003;**30**:2732–3.
- 11 **Garrett S**, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;**21**:2286–91.
- 12 **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.
- 13 **Maksymowych WP**, Jauregui E, Spady B, Russell AS. The Bath Ankylosing Spondylitis Disease Activity Index: Lack of discriminant ability between AS and mechanical low back pain [abstract]. European League Against Rheumatism Scientific Meeting, 12–15 June 2003, Lisbon, Portugal.
- 14 **de Vlam K**, Bokken A. BASDAI is unable to discriminate between inflammatory low back pain and mechanical low back pain [abstract]. *Ann Rheum Dis* 2005;**64**(suppl III):335.
- 15 **Taylor AL**, Balakrishnan C, Calin A. Centile reference charts for measures of disease activity, functional impairment, and metrology in ankylosing spondylitis. *Arthritis Rheum* 1998;**41**:1119–25.
- 16 **Barkham N**, Kong KO, Tennant A, Fraser A, Hensor E, Keenan AM, et al. The unmet need for anti-tumour necrosis factor (anti-TNF) therapy in ankylosing spondylitis. *Rheumatology* 2005;**44**:1277–81.
- 17 **Spoorenberg A**, van der Heijde D, de Klerk E, Dougados M, de Vlam K, Mielants H, et al. Relative value of the erythrocyte sedimentation rate and C-reactive protein in assessment of disease activity in ankylosing spondylitis. *J Rheumatol* 1999;**26**:980–4.
- 18 **Gorman JD**, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002;**346**:1349–56.
- 19 **Braun J**, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicentre trial. *Lancet* 2002;**359**:1187–93.
- 20 **Davis JC Jr**, van der Heijde D, Braun J, Dougados M, Cush J, Clegg DO, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;**48**:3230–6.
- 21 **Calin A**, Dijkmans BA, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, et al. Outcomes of a multicentre randomized clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis* 2004;**63**:1594–600.
- 22 **van der Heijde D**, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;**52**:582–91.
- 23 **Marzo-Ortega H**, McGonagle D, Jarrett S, Haugeberg G, Hensor E, O'Connor P, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. *Ann Rheum Dis* 2005;**64**:1568–75.
- 24 **Haibel H**, Rudwaleit M, Brandt HC, Grodzanovic Z, Listing J, Kupper H, et al. Adalimumab reduces spinal symptoms in active ankylosing spondylitis: clinical and magnetic resonance imaging results of a fifty-two-week open-label trial. *Arthritis Rheum* 2006;**54**:678–81.
- 25 **Ribbens C**, Martin y Porras M, Franchimont N, Franchimont N, Kaiser MJ, Jaspard JM, et al. Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment. *Ann Rheum Dis* 2002;**61**:161–6.
- 26 **Maksymowych WP**, Jhangri GS, Lambert RG, Mallon C, Buenviaje H, Pedrycz E, et al. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. *J Rheumatol* 2002;**29**:959–65.
- 27 **Vandooren B**, Kruijthof E, Yu DT, Rihl M, Gu J, De Rycke L, et al. Involvement of matrix metalloproteinases and their inhibitors in peripheral synovitis and down-regulation by tumor necrosis factor alpha blockade in spondyloarthritis. *Arthritis Rheum* 2004;**50**:2942–53.
- 28 **Yang C**, Gu J, Rihl M, Baeten D, Huang F, Zhao M, et al. Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. *Arthritis Rheum* 2004;**51**:691–9.
- 29 **Maksymowych WP**, Poole AR, Hiebert L, Webb A, Ionescu M, Lobanok T, et al. Etanercept exerts beneficial effects on articular cartilage biomarkers of degradation and turnover in patients with ankylosing spondylitis. *J Rheumatol* 2005;**32**:1911–17.
- 30 **Chen CH**, Lin KC, Yu DT, Yang C, Huang F, Chen HA, et al. Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in ankylosing spondylitis: MMP-3 is a reproducibly sensitive and specific biomarker of disease activity. *Rheumatology* 2006;**45**:414–20.
- 31 **Brandt J**, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000;**43**:1346–52.
- 32 **Drouart M**, Saas P, Billot M, Cedoz JP, Tiberghien P, Wendling D, et al. High serum vascular endothelial growth factor correlates with disease activity of spondyloarthropathies. *Clin Exp Immunol* 2003;**132**:158–62.
- 33 **Kim TH**, Stone M, Payne U, Zhang X, Ionescu M, Lobanok T, et al. Cartilage biomarkers in ankylosing spondylitis: relationship to clinical variables and treatment response. *Arthritis Rheum* 2005;**52**:885–91.
- 34 **Yilmaz N**, Ozaslan J. Biochemical bone turnover markers in patients with ankylosing spondylitis. *Clin Rheumatol* 2000;**19**:92–8.
- 35 **Toussirot E**, Ricard-Blum S, Dumoulin G, Cedoz JP, Wendling D. Relationship between urinary pyridinium cross-links, disease activity and disease subsets of ankylosing spondylitis. *Rheumatology* 1999;**38**:21–7.
- 36 **Marthofer W**, Stracke H, Masoud I, Scheja M, Graef V, Bolten W, et al. Evidence of impaired cartilage/bone turnover in patients with active ankylosing spondylitis. *Ann Rheum Dis* 1995;**54**:556–9.
- 37 **Visvanathan S**, Braun J, van der Heijde D, Marini JC, Han J, Gathany T, et al. Effect of infliximab on markers of inflammation and angiogenesis and correlations with improvement in spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis [abstract]. *Arthritis Rheum* 2005;**52**(suppl):S279.
- 38 **Park M-C**, Lee S-W, Choi S-T, Park Y-B, Lee S-K. Bone and cartilage turnover markers, bone mineral density, and radiographic damage in men with ankylosing spondylitis [abstract]. *Arthritis Rheum* 2005;**52**(suppl):S641.
- 39 **Kirshner B**, Guyatt G. A methodological framework for assessing health indices. *J Chronic Dis* 1985;**38**:27–36.
- 40 **Ward MM**. Evaluative laboratory testing. Assessing tests that assess disease activity. *Arthritis Rheum* 1995;**38**:1555–63.
- 41 **Braun J**, Baraliakos X, Golder W, Brandt J, Rudwaleit M, Listing J, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. *Arthritis Rheum* 2003;**48**:1126–36.
- 42 **Baraliakos X**, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. *Arthritis Rheum* 2005;**52**:1216–23.
- 43 **Rudwaleit M**, Baraliakos X, Listing J, Brandt J, Sieper J, Braun J. Magnetic resonance imaging of the spine and sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. *Ann Rheum Dis* 2005;**64**:1305–10.
- 44 **Sieper J**, Baraliakos X, Listing J, Brandt J, Haibel H, Rudwaleit M, et al. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab. *Rheumatology* 2005;**44**:1525–30.
- 45 **MacKay K**, Mack C, Brophy S, Calin A. The Bath Ankylosing Spondylitis Radiology Index (BASRI): a new, validated approach to disease assessment. *Arthritis Rheum* 1998;**41**:2263–70.
- 46 **Spoorenberg A**, de Vlam K, van der Linden S, Dougados M, Mielants H, van de Tempel H, et al. Radiological scoring methods in ankylosing spondylitis. Reliability and change over 1 and 2 years. *J Rheumatol* 2004;**31**:125–32.
- 47 **Wanders AJ**, Landewe RB, Spoorenberg A, Dougados M, van der Linden S, Mielants H, et al. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. *Arthritis Rheum* 2004;**50**:2622–32.
- 48 **van der Heijde D**, Landewe R, van der Linden S. How should treatment effect on spinal radiographic progression in patients with ankylosing spondylitis be measured? *Arthritis Rheum* 2005;**52**:1979–85.
- 49 **Boonen A**, van der Heijde D, Landewe R, Spoorenberg A, Schouten H, Rutten-van Malken M, et al. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Ann Rheum Dis* 2002;**61**:429–37.
- 50 **Boonen A**, Chorus A, Landewe R, van der Heijde D, Miedema H, van der Tempel H, et al. Manual jobs increase the risk of patients with ankylosing spondylitis withdrawing from the labour force, also when adjusted for job related withdrawal in the general population. *Ann Rheum Dis* 2002;**61**:658.
- 51 **Ward MM**. Functional disability predicts total costs in patients with ankylosing spondylitis. *Arthritis Rheum* 2002;**46**:223–31.
- 52 **Ward MM**, Kuzis S. Risk factors for work disability in patients with ankylosing spondylitis. *J Rheumatol* 2001;**28**:315–21.