The Burden of Ankylosing Spondylitis

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ABSTRACT. The acute as well as chronic clinical features of ankylosing spondylitis (AS) are a burden to the patient and society. Apart from the axial and articular manifestations, extraarticular AS-related comorbidities such as uveitis, inflammatory bowel disease, and psoriasis contribute to the burden of the disease. In addition, a large proportion of patients have osteoporosis or osteopenia, which may be associated with fractures and contribute to kyphosis. All these features result in decreased quality of life. Moreover, patients with AS have an increased mortality rate. The impact of this disease also can be seen in various aspects of workforce participation, from requiring more assistance at paid work to withdrawal from the workforce. Further, patients with AS and, subsequently, society are affected by substantial healthcare costs related to medications and healthcare provider expenses. Early diagnosis and management of patients will likely prevent functional disability and improve patient outcomes. (J Rheumatol 2006;33 Suppl 78:4-11)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS MORBIDITY MORTALITY COST OF ILLNESS

INTRODUCTION

Chronic diseases can adversely affect patients not only in terms of physical suffering, impaired function, and diminished quality of life, but can also have an impact on employment perspectives and out-of-pocket costs. In addition to the burden on the patient, a condition with a high prevalence can be a significant burden on society by increasing overall healthcare costs, non-healthcare costs, and disability payments due to withdrawal from the labor force.

Ankylosing spondylitis (AS) is a chronic condition that, depending on the geographical region studied, affects about 0.1% to 1.4% of the population[1-10]. It is characterized by chronic inflammation of the axial skeleton, particularly the sacroiliac joint[11,12]. Peripheral joints and extraarticular sites are also frequently involved[11,13]. Because the onset of AS can occur at a relatively young age, usually during early adulthood, patients have to adjust to their disease for most of their lives. Similarly to other chronic diseases, AS can affect quality of life, morbidity, mortality, participation in paid and unpaid work, and healthcare costs. We review the various domains that contribute to the burden of AS on the patient and society.

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Funding for this supplement was provided by Amgen Inc. and Wyeth Research.

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PHYSICAL FUNCTIONING AND QUALITY OF LIFE

A major clinical feature of AS is diminished physical functioning. The Bath Ankylosing Spondylitis Functional Index (BASFI) has shown that patients with AS have the greatest difficulty with activities requiring bending forward at the waist and being able to complete a full day of regular activity[14]. Cross-sectional and longitudinal studies have indicated that longer disease duration, increasing age, and smoking are associated with decreased functioning[15,16], whereas performing back exercises and having a greater degree of social support improves functioning[15]. Although it has been suggested that most of the loss in function occurs within the first 10 years of the onset of the disease[17], further longitudinal studies are required to fully elucidate the rate of progression of disability. The loss in function with AS contributes to self-reported feelings of lower vitality[18,19]. In addition, poorer function is also related to fatigue[19].

When applying a patient-reported disability measure in patients with rheumatoid arthritis (RA) and AS, their disease had a similar influence on overall function, although older RA patients (≥ 51 yrs) tended to report somewhat worse physical functioning than their age-matched counterparts with AS. However, when function was assessed using the Steinbrocker index, men with AS incurred a greater physical disability than men with RA[20]. As expected, with increasing age, both male and female patients with AS experienced reduced function, but the decline with increasing age was greater than in patients with RA. This difference can be partially explained by disease duration. The onset of AS is typically earlier than RA; therefore, in older age-matched patients, those with AS will have a longer disease duration than those with RA.

Not only is physical functioning diminished in patients with AS, but also their quality of life. With generic qual-

ity of life instruments, significant differences have been observed between AS patients and the general population, including all physical and psychosocial domains[21]. In addition, in an international longitudinal, observational study, a greater proportion of patients with AS reported moderate to severe limitations in mobility, self-care, daily activity, pain, and anxiety (the 5 EuroQoL domains) than reported in the general population (A. Boonen, unpublished data). In a study that included AS patients with high disease activity who were refractory to conventional treatment, patients with AS had lower scores in all domains of quality of life (Medical Outcome Survey Short Form-36) when compared with patients with hypertension, diabetes, or arthritis, and scores comparable to patients with chronic heart failure[21]. Further, the diminished social functioning experienced by patients with AS is similar to that seen in patients who have lost a limb. These results are not reflective of differences in age or sex ratios between conditions since the data were adjusted for these variables.

The impact of AS on quality of life is consistently shown not only in generic quality of life instruments[14,21-23], but also in studies that assess specific factors contributing to quality of life in AS. When asked to identify those areas that influence their quality of life, patients with AS are most concerned with factors such as stiffness, pain, fatigue, and poor sleep[23]. The Ankylosing Spondylitis Quality of Life (ASQoL) is a disease-specific quality of life instrument developed from interviews with AS patients. The items most often reported by patients were related to pain, fatigue, mood, sleep disturbance, and decreased functioning, especially related to household tasks, family activities, dressing, and personal hygiene[24]. As discussed below, having paid employment contributes to better physical and mental quality of life[25,26].

COMORBIDITIES AND EXTRAARTICULAR MANIFESTATIONS

Ankylosing spondylitis is associated with a variety of extraarticular manifestations that can result in a number of comorbid conditions (Table 1). Osteoporosis, one of the more common comorbid conditions, can ultimately result in vertebral fractures[27]. Studies indicate that 46% to 56% of patients with AS have a bone mineral density T-score ≤ -1.0 (measured at lumbar spine) and can be classified as osteoporotic or osteopenic[27,28]. Bone loss is higher in AS patients who are older and have longer disease duration[27].

Patients with AS are at heightened risk for sustaining a vertebral fracture. This is a result of decreased mechanical strength (as a consequence of osteoporosis), spinal rigidity, and kyphotic deformities[29]. In a population-based inception cohort in Minnesota, USA, the risk for thoracolumbar compression fractures was 7.6 (95% confidence interval 4.3–12.6) when compared with the population rates[30]. In another report, about 6% of patients with AS had sustained at least one vertebral fracture[31]. However, this value increases to 14% in patients with AS for 42 years or more. Forty-seven percent of patients with AS who experience a clinical cervical vertebral fracture experience some form of neurological complication, ranging from transient paresthesia to chronic loss of strength in the arms or legs[32]. Notably, 65% of patients with AS who experience a vertebral fracture do not recover completely from subsequent neurological complications.

Table 1. Clinical conditions contributing to the burden of ankylosing spondylitis.

	Prevalence*,%	Hazard Ratio†	Identified Risk Factors*
Morbidity as consequence of AS			
Low BMD[27,28]	46–56		Advancing age Disease duration
Kyphosis[34]	45††		Radiographic evidence of spinal damage Disease activity (BASDAI)
Vertebral fracture[30,31]	6	7.6 (95% CI 4.2-12.6)	
Myocardial infarction[38]		1.44 (95% CI 1.15-1.81)	
AS-related comorbid conditions			
Uveitis[41]	20–30		
Psoriasis[47]	9		
IBD[46,47]	1–6		

*Among patients with ankylosing spondylitis. †Compared with the normal population. ††Defined as occiput–wall distance > 0. AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMD: bone mineral density; IBD: inflammatory bowel disease.

Later in the course of the disease, patients may lose their normal spinal posture and develop thoracic kyphosis[12]. The degree of kyphosis is related to spinal deformity resulting from vertebral fractures and due to wedging of the intervertebral discs[33]. In a cross-sectional study, patients with kyphosis were older and had lower physical functioning[34]. In addition, kyphosis was seen in a greater percentage of men than women. Factors that independently contributed to the degree of kyphosis (measured by mean vertebral wedging) included radiographic evidence of spinal damage and disease activity[34].

These changes that occur in the spine predispose patients to spinal cord injuries. In a study of the Finnish population, patients with AS sustained spinal cord injuries at a rate 11 times greater than the general population[29]. Slipping was cited as the cause of the trauma in over half the patients with AS who sustained a spinal cord injury versus 7% in the whole population of patients with traumatic spinal cord injuries.

The additional risk of cardiovascular disease noted in patients with AS[35] is now receiving further attention. Aortic insufficiency, conduction disturbances, diastolic disturbances, cardiomyopathy, and pericarditis are significantly associated with AS[36,37]. Men with AS also have a higher rate of first-time myocardial infarctions than men without AS[38]. A study in Norway reported that patients with AS or related spondyloarthropathies (SpA) underwent their first coronary artery bypass graft at a significantly earlier age than those without SpA. Moreover, AS/SpA is a stronger predictor of aortocoronary bypass at a young age than the traditional cardiovascular risk factors[39].

Uveitis, psoriasis, and inflammatory bowel disease (IBD) are well recognized disease-related manifestations[40]. There is a 20% to 40% likelihood of the occurrence of one or more attacks of acute anterior uveitis in patients with AS[41,42]. In some patients it may become chronic or result in visual impairment[43]. Uveitis can also influence physical functioning. In a longitudinal study (duration up to 6 yrs), patients with AS who had uveitis had a significant decline in BASFI scores compared with patients without uveitis[44]. Patients with eye involvement also have greater radiologic changes of the axial skeleton than AS patients without uveitis[45]. An estimated 1% to 6% of patients with AS will also have IBD[46,47], and about 9% will have psoriasis[47]. Patients with AS who also have psoriasis and/or IBD have a higher degree of disease activity and lower physical functioning compared with those patients who do not have these comorbid conditions[45].

MORTALITY

Population studies that include patients with varying degrees of disease activity have shown no increase in mortality rate between AS patients and the general population[48,49]; however, other reports describe decreased survival in AS patients. Although it is no longer considered a viable treatment option, some older patients with AS have undergone radiotherapy, which may affect their longterm survival. Therefore, it may not be surprising that those who received radiotherapy have a mortality rate higher than the general population or the nonirradiated AS population[49-51]. When nonirradiated patients from hospitals or rheumatology clinics were evaluated, those with AS had a higher mortality rate than expected from the general population[35,52,53]. The discrepancy between the results in population studies versus those that selected patients from clinics and hospitals may be due to differences in disease activity. Patients in clinics and hospitals may have a higher degree of disease activity; whereas in the population studies, there is a greater inclusion of patients with mild disease[54-56].

There may be many underlying causes for the increase in mortality rate seen in patients with AS, especially those with more severe disease. For instance, severe spinal conditions associated with AS (e.g., bamboo deformity, kyphoscoliosis, and cervical flexion) can lead to respiratory difficulties and contribute to death[57]. Although amyloidosis is now a rare complication of AS, it was cited as the cause of AS-related death in 70% of cases reported in a Finnish study[52]. Cardiovascular disease is often listed as the cause of death in many patients with AS[36]. In addition, a study indicated that patients with AS are more likely to die of an accident or violence than those in the healthy Finnish population[57].

LOSS OF PRODUCTIVITY

Patients with AS have lower employment rates, incur more official work disability, and experience more absences from work than the general population[58,59]. Figures 1 and 2 summarize the findings of 14 studies (13 cross-sectional and 1 cohort) that included either employment or work disability among work-related outcomes and at the same time provided the disease duration of the studied sample. Reported employment of patients with AS ranges from 55% (in The Netherlands) to 89% (in Finland)[20,60-63]. In a study conducted in the US, 13% of patients with a median disease duration of 21 years had left the labor force[62], compared with 36% in France[54] and 31% in The Netherlands[64]. In The Netherlands, patients with AS were 3 times more likely to withdraw from the labor force than expected in the general population[64], and this was more pronounced in patients with a manual job[65]. Differences in the economic environment[59] or social security system[63] have been identified as factors that may explain some differences seen in the employment of patients with AS in different countries.

The employment status of patients can influence their

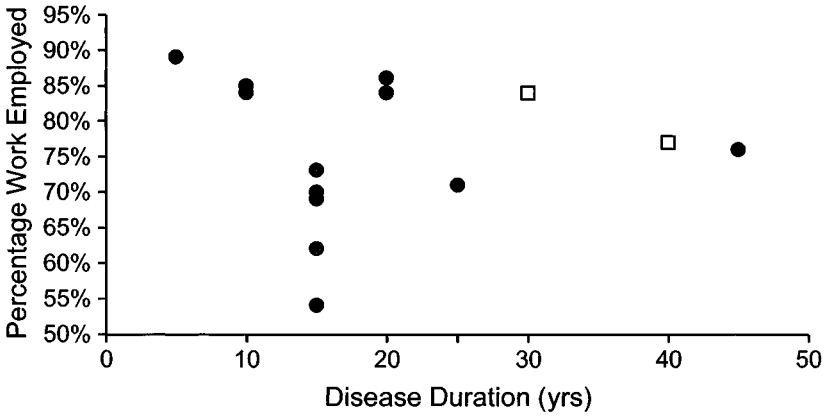

Figure 1. Proportion of patients employed as a function of disease duration. Summary of data reported in 14 cross-sectional studies. Squares represent data from 1 study that reported 2 followup points with different disease durations.

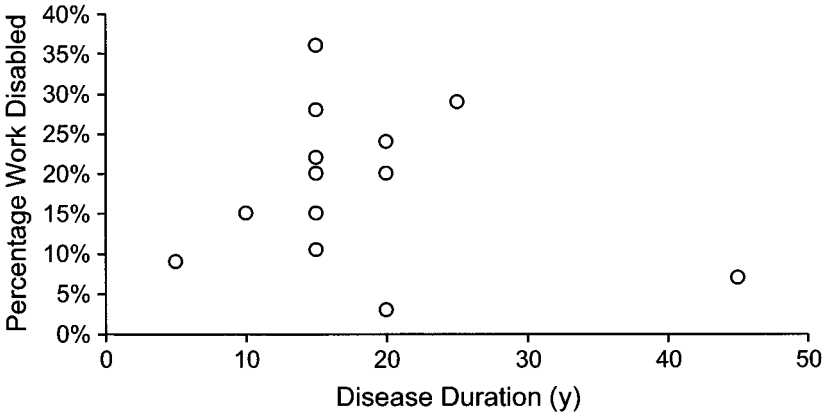

Figure 2. Proportion of patients work disabled as a function of disease duration. Summary of data reported in 13 cross-sectional studies and 1 cohort study.

Table 2. Risk factors associated with diminished work status.

	Reduced Hours[62*]	Requiring Assistance[62*]	Episodes of Sick Leave[63*]	Duration of Sick Leave[25,54,62*,63*]	Changing Job[62*]	Work Disability[62*]	Withdrawal[25,54,58,64-66]
Manual labor		●	●	●	●	●	●
Other job characteristics							●
Disability	●	●	●	●			
Sex	● (F)				● (F)		● ††
Pain	●	●		●	●		
Comorbid condition				● †		●	
Socioeconomic environment			●			●	
Disease activity				●			
Older age of disease onset						●	●
Education						●	
Passive coping strategies							●

*Outcomes were prospectively assessed. †Specific for inflammatory bowel disease. F: female; ††inconsistent for sex.

quality of life. Studies have consistently demonstrated that patients who are no longer employed have a lower quality of life[22,26,64].

Factors associated with various aspects of employment are summarized in Table 2. Consistently, manual labor (Figure 3)[25,62,65,66], age at onset of disease[62,64], and passive avoidance coping strategies independently influence employment[64]. In addition, women and those with comorbid conditions have a greater likelihood of receiving disability compensation[62]. Although gender may influence employment, it does not appear to be an independent factor in all studies that examine the influence of gender[58,64,65]. With increasing disease duration, more patients become work disabled. However, the risk of becoming work disabled when compared with the general population is especially increased in younger patients[64]. Anecdotal evidence indicates that fatigue is the major concern of patients in terms of maintaining full employment[61]. Other concerns cited included pain, limited mobility, and the unpredictability of symptoms. However, many patients could continue their employment if technical or ergonomic adjustments were available[25,54].

Even when patients continue in a salaried position, AS adversely affects their workplace performance. In Europe, about half of patients with AS report having to take sick leave (at least 1 day in duration) related to their disease[63]. In the US, 15% had long periods of sick leave over a period of 4 years[62]. Having a position requiring manual labor or having a greater degree of disability independently predicts the occurrence of sick leave[63]. On the other hand, the length of each sick leave episode is longer for those patients with higher disease activity (Bath Ankylosing Spondylitis Disease Activity Index)[63], greater functional disability[62], IBD[63], and higher levels of pain[62]. With increasing functional disability, pain, or physically demanding activities there is a 2 to 5 times greater need for assistance[62]. Women are more likely to switch to a less physically demanding position or decrease their hours than men[62]. In addition, patients who report a higher degree of pain and have a more physically demanding position are at greater risk of switching jobs.

In addition to loss of productivity in paid employment, many patients with AS need to spend time resting, exercising, or attending a healthcare clinic. These activities can reduce the time available for other activities by an average of 1.25 hours per day[67]. With increasing disease activity and worsening function, the amount of work time lost to these activities increases.

In summary, AS clearly diminishes all domains of work status for patients (Table 2). The economic environment and social security system in which the patients live have an important influence on the absolute figures on work participation. Independent of the socioeconomic environment, patients who are employed in a position requiring manual labor or who have greater physical limitations or pain are at greater risk of experiencing some loss in productivity than those in professional positions or those in whom the disease has not progressed to the point of limitation in physical functioning.

HEALTHCARE COSTS

Costs associated with a disease include direct and indirect (productivity) costs. Direct costs include expenses incurred obtaining medical services or treatment for the disease (including visits to healthcare providers, hospitalizations, treatments, assistive devices, and paid or unpaid household help). Indirect costs encompass the expenses incurred with loss of productivity, which were described in the previous section. It is often difficult to compare direct costs between countries, mainly due to price differences for healthcare resources. Further, studies vary in

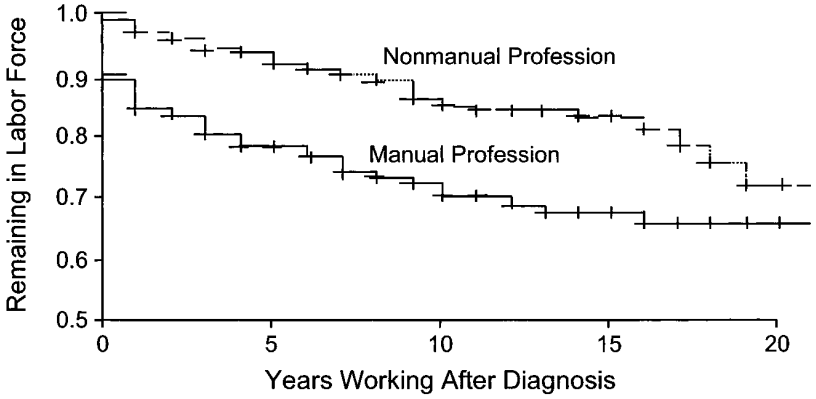

Figure 3. Influence of type of profession on unemployment in patients with AS. The probability of remaining in the work force is represented by Kaplan-Meier curves for those employed in manual versus nonmanual positions. From Boonen A, *et al.* Ann Rheum Dis 2001;60:1033-9, with permission.

Table 3. Average annual costs associated with AS (2003 US dollars)*. Adapted from Boonen and van der Heijde. Expert Rev Pharmacoeconomics Outcomes Res 2005;5:163-81, with permission.

	United States[69]	United Kingdom[16]	European Tri-nation†[70]
Direct costs	1913	4478	3307
Indirect costs	5287	6143	8535
Total costs††	7243	10,620	11,843

*As adjusted for differences in timing of consumer price indices and purchasing power parities.
†Nations studied: France, Belgium, The Netherlands.
††Studied using the human capital method.

design, type of patients included, and data collection. Even with these limitations, it is clear that there is a substantial societal cost related to the medical treatment of AS. After converting to US dollars (2003) and adjusting for differences in timing of consumer price indices and purchasing power parities, direct costs ranged from $1913 in the US to $4478 in the United Kingdom. Total indirect costs associated with AS account for 73% and 58% of the total costs and range from $5287 in the US to $8535 in Europe (Table 3)[68]. In the US, medications account for 42% of the direct costs associated with AS; ambulatory and hospital care account for 15% and 16%, respectively[62]. Costs associated with ambulatory and hospital care (21%–31% and 2%–27%, respectively) account for a greater percentage of direct costs in studies performed in European nations[68]. The costs associated with medications contributed only 6% to 12.5% to the direct costs associated with AS in these studies.

In the US, women and patients with greater functional disability have higher annual direct costs associated with their disease[69]. In European studies, higher costs are incurred by patients who have longer duration of disease, higher disease activity, lower physical functioning, and a lower level of formal education[16,70]. Also, patients who have extraspinal disease manifestations incur higher direct costs[70].

In terms of costs to the patient, a study of 3 European nations indicated that the greatest percentage of costs came from loss of income[67]. Further, non-healthcare costs, such as private household help, transportation, and exercise, accounted for 64% of out-of-pocket (non-healthcare) expenses. Significant differences were seen between countries, which are most likely due to differences in national healthcare policy.

It is important to note that these studies were performed before the approval of biologic agents for the treatment of AS. Further studies are needed to determine the effects of biologic therapy on overall disease costs. Studies modeling the cost-effectiveness of the biologic agents are addressed in the following section.

COST-EFFECTIVE TREATMENT

A limited number of studies have evaluated the cost-utility of treatments in patients with AS. In these studies, the additional costs incurred by the new treatment are weighted against the extra gain in utility, resulting in a cost-utility ratio. Comparing the added benefits of 3 weeks of spa therapy in Austria or The Netherlands with standard care (weekly group exercise), the spa therapy had favorable cost-benefit and cost-utility ratios[71]. The additional costs of spa therapy were partly offset by lower costs associated with healthcare providers, physiotherapy, and medications as compared with standard treatment and resulted in a substantial gain in utility.

Another study evaluated the cost-effectiveness of inhibiting tumor necrosis factor-α. Data on effectiveness were based on a German infliximab trial and data on costs and utilities were derived from a cross-sectional observation of patients in the United Kingdom. The longterm (30 yr) treatment with infliximab was projected to result in a cost of less than £10,000 per quality-adjusted life-year (QALY) gained[16] if both direct and indirect costs were considered. However, in the model that included direct costs only or that applied a short-term time horizon, the cost per QALY was substantially higher. Whether these ratios are acceptable will depend upon regional thresholds that are applied by decision makers to judge an intervention as cost-effective.

The issue of cost-utility of treatment of AS with biologics is also addressed in a recent Markov study[72]. It needs to be stressed that modeling of data to estimate costs per QALY of treatment with biologics in AS has limitations. It can be expected that early diagnosis and recognition of patients at risk for severe disease course will enable selection of patients who will derive longterm benefits from early aggressive treatment, leading to savings in future healthcare and productivity costs. Further, clinical trials with biological therapies included patients with AS with long disease duration who had adapted to their disease, and the possible gain in utility has been underestimated. These points should be taken into account when modeling the cost-utility and considering reimbursement, otherwise, the estimated costs per QALY will be inflated. Future research should concentrate on studying factors that predict severe disease course and the correct assessment of the longterm loss of utility. The better we are able to predict prognosis, the more cost-effective our treatments will be.

CONCLUSION

Ankylosing spondylitis is a chronic disease that lowers the physical function of patients, thereby reducing their quality of life. Patients with AS may also have an increased mortality rate compared with the general population and an increased risk of comorbid conditions.

The clinical burden of disease results in significant direct and indirect costs to the patient and the healthcare system. As discussed elsewhere in this supplement series, effective treatments to reduce the symptoms of AS are available. In order to offer effective treatment, however, patients with AS must be diagnosed early, and patients with poor prognosis must be identified. Because functional disability is the main contributor to the burden associated with AS, it is important that patients at risk for a severe course of disease are recognized and treated in a timely manner.

ACKNOWLEDGMENT

The authors wish to thank Debra Stamper, PhD, whose work was funded by Amgen, Inc., for providing assistance in the drafting of this report, and Scott Baumgartner, MD, of Amgen Inc. for contributing to the concept development.

REFERENCES

1. Gran JT, Husby G, Hordvik M. Prevalence of ankylosing spondylitis in males and females in a young middle-aged population of Tromso, northern Norway. Ann Rheum Dis 1985;44:359-67.
2. Kaipiainen-Seppanen O, Aho K, Heliovaara M. Incidence and prevalence of ankylosing spondylitis in Finland. J Rheumatol 1997;24:496-9.
3. Alamanos Y, Papadopoulos NG, Voulgari PV, Karakatsanis A, Siozos C, Drosos AA. Epidemiology of ankylosing spondylitis in Northwest Greece, 1983-2002. Rheumatology Oxford 2004;43:615-8.
4. Boyer GS, Templin DW, Cornoni-Huntley JC, et al. Prevalence of spondyloarthropathies in Alaskan Eskimos. J Rheumatol 1994;21:2292-7.
5. Braun J, Bollow M, Remlinger G, et al. Prevalence of spondyloarthropathies in HLA-B27 positive and negative blood donors. Arthritis Rheum 1998;41:58-67.
6. Dai SM, Han XH, Zhao DB, Shi YQ, Liu Y, Meng JM. Prevalence of rheumatic symptoms, rheumatoid arthritis, ankylosing spondylitis, and gout in Shanghai, China: a COPCORD study. J Rheumatol 2003;30:2245-51.
7. Hukuda S, Minami M, Saito T, et al. Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. J Rheumatol 2001;28:554-9.
8. van der Linden SM, Valkenburg HA, de Jongh BM, Cats A. The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. Arthritis Rheum 1984;27:241-9.
9. Trontzas P, Andrianakos A, Miyakis S, et al. Seronegative spondyloarthropathies in Greece: a population-based study of prevalence, clinical pattern, and management. The ESORDIG study. Clin Rheumatol 2005;24:583-9.
10. Akkoc N, Khan MA. Overestimation of the prevalence of ankylosing spondylitis in the Berlin study: Comment on the article by Braun et al. Arthritis Rheum 2005;52:4048-9.
11. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002;61 Suppl:iii8-18.
12. van der Linden S, van der Heijde D, Braun J. Ankylosing spondylitis. In: Harris EJ, Budd R, Firestein GS, Genovese MC, Sergent JS, Sledge CB, editors. Kelly's textbook of rheumatology. 7th ed. Philadelphia: Elsevier Saunders; 2005:1125-41.
13. Khan MA. Update on spondyloarthropathies. Ann Intern Med 2002;136:896-907.
14. Ariza-Ariza R, Hernandez-Cruz B, Navarro-Sarabia F. Physical function and health-related quality of life of Spanish patients with ankylosing spondylitis. Arthritis Rheum 2003;49:483-7.
15. Ward MM. Predictors of the progression of functional disability in patients with ankylosing spondylitis. J Rheumatol 2002;29:1420-5.
16. Kobelt G, Andlin-Sobocki P, Brophy S, Jonsson L, Calin A, Braun J. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). Rheumatology Oxford 2004;43:1158-66.
17. Gran JT, Skomsvoll JF. The outcome of ankylosing spondylitis: a study of 100 patients. Br J Rheumatol 1997;36:766-71.
18. Dagfinrud H, Vollestad NK, Loge JH, Kvien TK, Mengshoel AM. Fatigue in patients with ankylosing spondylitis: A comparison with the general population and associations with clinical and self-reported measures. Arthritis Rheum 2005;53:5-11.
19. van Tubergen A, Coenen J, Landewe R, et al. Assessment of fatigue in patients with ankylosing spondylitis: a psychometric analysis. Arthritis Rheum 2002;47:8-16.
20. Zink A, Braun J, Listing J, Wollenhaupt J. 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.
21. Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum 2005;53:494-501.
22. Ozgul A, Peker F, Taskaynatan MA, Tan AK, Dincer K, Kalyon TA. Effect of ankylosing spondylitis on health-related quality of life and different aspects of social life in young patients. Clin Rheumatol 2006;25:168-74. Epub 2005 Aug 10.
23. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res 1999;12:247-55.
24. Doward LC, Spoorenberg A, Cook SA, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6.
25. Chorus AM, Boonen A, Miedema HS, van der Linden S. Employment perspectives of patients with ankylosing spondylitis. Ann Rheum Dis 2002;61:693-9.
26. Chorus AM, Miedema HS, Boonen A, van der Linden S. Quality of life and work in patients with rheumatoid arthritis and ankylosing spondylitis of working age. Ann Rheum Dis 2003;62:1178-84.
27. El Maghraoui A. Osteoporosis and ankylosing spondylitis. Joint Bone Spine 2004;71:291-5.
28. El Maghraoui A, Borderie D, Cherruau B, Edouard R, Dougados M, Roux C. Osteoporosis, body composition, and bone turnover in ankylosing spondylitis. J Rheumatol 1999;26:2205-9.
29. Alaranta H, Luoto S, Konttinen YT. Traumatic spinal cord injury as a complication to ankylosing spondylitis. An extended report. Clin Exp Rheumatol 2002;20:66-8.
30. Cooper C, Carbone L, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ 3rd. Fracture risk in patients with ankylosing spondylitis: a population based study. J Rheumatol 1994;21:1877-82.
31. Feldtkeller E, Vosse D, Geusens P, van der Linden S. Prevalence and annual incidence of vertebral fractures in patients with ankylosing spondylitis. Rheumatol Int 2006;26:234-9.
32. Vosse D, Feldtkeller E, Erlendsson J, Geusens P, van der Linden S. Clinical vertebral fractures in patients with ankylosing spondylitis. J Rheumatol 2004;31:1981-5.
33. Geusens P, Vosse D, van der Heijde D, et al. High prevalence of thoracic vertebral deformities and discal wedging in ankylosing spondylitis patients with hyperkyphosis. J Rheumatol

2001;28:1856-61.
34. Vosse D, van der Heijde DM, Landewe RB, et al. Determinants of hyperkyphosis in patients with ankylosing spondylitis. Ann Rheum Dis 2006;65:770-4. Epub 2005 Oct 11.
35. Khan MA, Khan MK, Kushner I. Survival among patients with ankylosing spondylitis: a life-table analysis. J Rheumatol 1981;8:86-90.
36. Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum 2004;34:585-92.
37. Sun JP, Khan MA, Farhat AZ, Bahler RC. Alterations in cardiac diastolic function in patients with ankylosing spondylitis. Int J Cardiol 1992;37:65-72.
38. Symmons D, Goodson N, Cook M, Watson D. Men with ankylosing spondylitis have an increased risk of myocardial infarction [abstract]. Arthritis Rheum 2004;50 Suppl:S477.
39. Hollan I, Almdahl SM, Halvorsen P, Mikkelsen K, Saatvedt K, Forre O. Spondylarthropathies — a stronger predictor of aorto-coronary bypass at young age than traditional cardiovascular risk factors [abstract]. Arthritis Rheum 2005;52 Suppl:S213.
40. Khan MA. Spondyloarthropathies. In: Hunder GG, editor. Atlas of rheumatology. Philadelphia: Current Medicine; 2005:151-80.
41. Banares A, Hernandez-Garcia C, Fernandez-Gutierrez B, Jover JA. Eye involvement in the spondyloarthropathies. Rheum Dis Clin North Am 1998;24:771-84, ix.
42. Khan MA. Spondyloarthropathies. In: Hunder GG, editor. Atlas of rheumatology. Philadelphia: Current Medicine; 2002:141-67.
43. Kotaniemi K, Aho K, Kotaniemi A. Uveitis as a cause of visual loss in arthritides and comparable conditions. J Rheumatol 2001;28:309-12.
44. Robertson LP, Davis MJ. A longitudinal study of disease activity and functional status in a hospital cohort of patients with ankylosing spondylitis. Rheumatology Oxford 2004;43:1565-8.
45. Brophy S, Pavy S, Lewis P, et al. Inflammatory eye, skin, and bowel disease in spondyloarthritis: genetic, phenotypic, and environmental factors. J Rheumatol 2001;28:2667-73.
46. Baeten D, De Keyser F, Mielants H, Veys EM. Ankylosing spondylitis and bowel disease. Best Pract Res Clin Rheumatol 2002;16:537-49.
47. Edmunds L, Elswood J, Kennedy LG, Calin A. Primary ankylosing spondylitis, psoriatic and enteropathic spondyloarthropathy: a controlled analysis. J Rheumatol 1991;18:696-8.
48. Carter ET, McKenna CH, Brian DD, Kurland LT. Epidemiology of ankylosing spondylitis in Rochester, Minnesota, 1935-1973. Arthritis Rheum 1979;22:365-70.
49. Carbone LD, Cooper C, Michet CJ, Atkinson EJ, O'Fallon WM, Melton LJ, 3rd. Ankylosing spondylitis in Rochester, Minnesota, 1935-1989. Is the epidemiology changing? Arthritis Rheum 1992;35:1476-82.
50. Weiss H, Darby S, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. Int J Cancer 1994;59:327-38.
51. Darby SC, Doll R, Gill SK, Smith PG. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987;55:179-90.
52. Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. Ann Rheum Dis 1993;52:174-6.
53. Radford EP, Doll R, Smith PG. Mortality among patients with ankylosing spondylitis not given X-ray therapy. N Engl J Med 1977;297:572-6.
54. Guillemin F, Briancon S, Pourel J, Gaucher A. Long-term disability and prolonged sick leaves as outcome measurements in ankylosing spondylitis. Possible predictive factors. Arthritis Rheum 1990;33:1001-6.
55. Gran JT, Husby G. Ankylosing spondylitis: a comparative study of patients in an epidemiological survey, and those admitted to a department of rheumatology. J Rheumatol 1984;11:788-93.
56. Gran JT, Hordvik M, Husby G. Roentgenological features of ankylosing spondylitis. A comparison between patients attending hospital and cases selected through an epidemiological survey. Clin Rheumatol 1984;3:467-72.
57. Myllykangas-Luosujarvi R, Aho K, Lehtinen K, Kautiainen H, Hakala M. Increased incidence of alcohol-related deaths from accidents and violence in subjects with ankylosing spondylitis. Br J Rheumatol 1998;37:688-90.
58. Boonen A, Chorus A, Miedema H, van der Heijde D, van der Tempel H, van der Linden S. Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients. Ann Rheum Dis 2001;60:353-8.
59. Mau W, Listing J, Huscher D, Zeidler H, Zink A. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol 2005;32:721-8.
60. Boonen A, de Vet H, van der Heijde D, van der Linden S. Work status and its determinants among patients with ankylosing spondylitis. A systematic literature review. J Rheumatol 2001;28:1056-62.
61. Barlow JH, Wright CC, Williams B, Keat A. Work disability among people with ankylosing spondylitis. Arthritis Rheum 2001;45:424-9.
62. Ward MM, Kuzis S. Risk factors for work disability in patients with ankylosing spondylitis. J Rheumatol 2001;28:315-21.
63. Boonen A, van der Heijde D, Landewe R, et al. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. Ann Rheum Dis 2002;61:429-37.
64. Boonen A, Chorus A, Miedema H, et al. Withdrawal from labour force due to work disability in patients with ankylosing spondylitis. Ann Rheum Dis 2001;60:1033-9.
65. Boonen A, Chorus A, Landewe R, 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 [letter]. Ann Rheum Dis 2002;61:658.
66. Roussou E, Kennedy LG, Garrett S, Calin A. Socioeconomic status in ankylosing spondylitis: relationship between occupation and disease activity. J Rheumatol 1997;24:908-11.
67. Boonen A, van der Heijde D, Landewe R, et al. Costs of ankylosing spondylitis in three European countries: the patient's perspective. Ann Rheum Dis 2003;62:741-7.
68. Boonen A, van der Heijde D. Review of the costs of illness of ankylosing spondylitis and methodologic notes. Expert Rev Pharmacoeconomics Outcomes Res 2005;5:163-81.
69. Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. Arthritis Rheum 2002;46:223-31.
70. Boonen A, van der Heijde D, Landewe R, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. Ann Rheum Dis 2003;62:732-40.
71. van Tubergen A, Boonen A, Landewe R, et al. Cost effectiveness of combined spa-exercise therapy in ankylosing spondylitis: a randomized controlled trial. Arthritis Rheum 2002;47:459-67.
72. Boonen A, van der Heijde D, Severens JL, et al. Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis. Ann Rheum Dis 2006;65:201-8.