Costs and Quality of Life of Patients with Ankylosing Spondylitis in Canada

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ABSTRACT. ***Objective***. The use of biological agents in the treatment of ankylosing spondylitis (AS) has emphasized the need for information about the current burden of the disease to estimate the cost-effectiveness of these drugs. We investigated resource utilization and utility of patients with AS in Canada.

Methods. A cross-sectional retrospective observational study was performed in a cohort of 545 patients with AS in Alberta, Ontario, British Columbia, and Manitoba. Patients completed a questionnaire asking about their healthcare consumption, out of pocket expenses, work capacity, and need for informal care during the past 3 months. Patients' current functional status and disease activity level was assessed using the Bath AS functional and disease activity indexes (BASFI and BASDAI), and utility was determined using the EQ-5D 5-dimensional health status classification. Descriptive analysis was performed to estimate costs and utility for the sample and by level of disease severity.

Results. Patients' mean age was 49.6 years and the mean disease duration was 22.3 years; 64% were male, and 63% of patients in the sample were working. The mean BASDAI score was 4.3 and BASFI 3.6, although 13% of patients in the sample had a BASFI score ≥ 7. The mean annual cost per patient is estimated at Cdn $9,008 (SD $17,724), and direct healthcare represented 28.9% of these costs. Patients' out of pocket costs represented 33.1%, and lost work capacity accounted for 38%. Costs increased significantly with diminishing physical function and high disease activity, covering a range of $4,000 to $30,000 per patient and year. The estimated cost-increase per unit-increase in the BASFI score at values < 5 was around $1,000, and more than $5,000 at values > 7. The mean utility was 0.65 (SD 0.23). Utility was significantly correlated with age, sex, BASFI, and BASDAI, covering a range from 0.87 for patients with BASFI/BASDAI ≤ 2 to 0.20 for patients with BASFI/BASDAI ≥ 8. On average, utility decreased by 0.075 for each unit-increase in the BASFI.

Conclusion. All types of costs accelerate steeply with increasing loss of function (BASFI) and disease activity (BASDAI) in patients with AS, while utility decreases significantly. Treatments that control disease activity and maintain patients' function are likely to offset the high cost and low quality of life of severe disease. Our findings provide information on the burden of AS and a baseline for assessing the cost-effectiveness of the new biological agents in this indication. (J Rheumatol 2006;33:289–95)

Key Indexing Terms:
COST OF ILLNESS UTILITY ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic inflammatory progressive disease characterized by pain, joint stiffness, and a gradual loss of spinal mobility that can lead to severe functional limitations[1,2]. The disease is thought to have onset in late adolescence, but is most often diagnosed in young adults. The impact of the disease, particularly the gradual onset of physical impairment, on work capacity and healthcare costs has been reported[3-5]. Similarly, patients' quality of life (QOL) is reduced as a consequence of both the loss of physical function and the pain linked to disease activity[6-9].

Treatment options for AS were until recently limited to physiotherapy to prevent the loss of mobility, antiinflammatory drugs to control the inflammatory process, and ultimately joint replacement[10,11]. As a consequence, treatment costs are limited and the cost of AS is currently driven by other costs such as productivity losses and patients' private investments to facilitate daily living. Total direct costs per patient and year in 3 European countries have been estimated at €2640 (Cdn $4,300; €1 = Cdn $1.63; all dollar costs are Canadian, unless otherwise specified), ranging between €1,800 and €2,800 (Belgium, Netherlands, France)[12,13] and at US $1,750 in the United States ($2,100; US $1 = Cdn $1.21)[3]. Productivity losses dominated costs, and total societal costs in these studies were estimated at €9,460 ($15,400) and US $6,720 ($8,130)[14]. The most recent study in the United Kingdom has estimated total annual costs at £6,776 per patient ($15,600; £1 = Cdn $2.30). Of these, only

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one-quarter was accounted for by direct healthcare costs, while 58% was due to productivity losses and 16.5% to investments and informal care[15].

Recently, anti-tumor necrosis factor-α (TNF-α) therapies have been shown to be very efficacious in the treatment of AS[15-18], but their cost is substantially higher than current treatments. As a consequence, direct costs of AS will increase, and the additional cost will have to be weighed against the health gains obtained with treatment. To perform such an analysis, current data on costs and the effects of the disease on patients' quality of life are required.

Our objective was to assess resource consumption, work capacity, and QOL (utility) of patients with AS in Canada, and to relate costs and utility to different levels of severity of the disease as potential baseline data for cost-effectiveness analysis.

MATERIALS AND METHODS

We performed a cross-sectional retrospective survey where information was collected directly from patients. A questionnaire developed for a study in the United Kingdom[8] was adapted to the Canadian setting. The questionnaire asked about patients' consumption of healthcare and community services related to AS during the past 3 months, out of pocket expenses such as over the counter (OTC) medication, assistive devices and investments (e.g., changes to the car or the house), informal care needs, and work capacity (changes in work situation, short and longterm sick leave, and early retirement). Utility was assessed using the EQ-5D 5-dimensional health status classification[19,20] in order to ensure comparability to the study in the UK. Functional impairment and disease activity were assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI)[21] and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[22], respectively.

All the academic and community-based rheumatology centers in Northern Alberta, the Ontario Spondylitis Association (OSA), and The Arthritis Society [British Columbia (BC) division] participated in the study. The names and addresses of all the 795 AS patients who had been in contact at least once with the rheumatology sites in Northern Alberta for the past 15 years were selected. These included patients that attended both community and academic-based rheumatologists. The OSA invited all their 273 patient-members to participate in the study and forwarded the invitation to 44 patient-members from Manitoba. The BC division of The Arthritis Society forwarded the invitation to 137 AS members. A total of 1249 questionnaires were mailed in April and May 2003. Questionnaires were fully anonymous and one reminder was sent about 4 weeks after the initial mailing to those who had not yet returned the completed questionnaire to the coordinating University of Alberta rheumatology center in a prepaid envelope. Data were entered at the coordinating center on a continuing basis and the database was locked 12 weeks after the mailing. Unit costs for the individual resources were taken from publicly available sources. Prescription drug costs were based on the standard recommended daily dose [*Compendium of Pharmaceuticals and Specialties 2004* (CPS)[23]] and prices were obtained from the *Liste de médicaments du Quebec* (RAMQ; 15th ed.)[24] or the PPS Pharma Publication Manual (July 2004). When available on the Formulary, generic prices were used. OTC medication was included at the cost indicated by the patients, after verification of a small number of products.

Costs for medical and surgical admission, outpatient attendance, and community and other services were obtained from the existing case-cost database of the London Health Sciences Centre (LHSC; London, Ontario, Canada). LHSC is a tertiary care teaching hospital and was an original participant in the Ontario Case Cost Project, and maintains a fully allocated database indexed by individual patient encounter with regular auditing and quality assurance. Rates of physician reimbursement for these services were obtained from the Ontario Hospital Insurance Plan (OHIP) Schedule of Benefits (July 2001).

Informal care was considered a direct cost and estimated using the replacement method (i.e., the cost of community care). Out of pocket expenses were counted as indicated by patients, as particularly for example for investments, it is impossible to estimate a standard unit cost. Loss of work capacity included sick leave, reductions in working time due to AS, and early retirement, and was estimated using an hourly wage of $19.78 for men and $16.27 for women (www.statcan.ca/english/Pgdb/labr69a.htm, August 2004).

Three-month resource consumption was multiplied by 4 to obtain one-year costs, with the rationale that a similar percentage of patients would consume these quantities of resources in any given 3-month period. Descriptive analysis was performed and mean annual costs per patient and for different levels of disease severity were estimated. Utilities were analyzed using the UK health status tariff[20].

RESULTS

Patient demographics. Within 12 weeks, 545 completed questionnaires were received (45%), and no patient had to be excluded due to a large amount of missing data. Demographics of the sample are presented in Table 1. The mean age of respondents was 49.9 years with a mean disease duration of 22.3 years. The mean BASDAI was 4.33 and the mean BASFI 3.56, and the full range of the 2 scales was covered (1–10). Mean utility was 0.65 (SD 0.23) and the mean score on the EuroQol visual analog scale (range 0 worst to 100 best) was 67.2 (SD 17.4).

A large proportion of patients came from Alberta and Ontario, and samples from BC and Manitoba may be too limited to make valid comparisons across provinces. However, patients from these 2 provinces were slightly older and had more severe functional impairment, particularly in BC. As a consequence, utility scores in these 2 provinces were lower. Also, the proportion of women in the sample from BC was surprisingly high.

The majority of patients were under 65 years of age (86%) and almost half had no or minimal functional impairment (BASFI < 3). Consequently, 63% of patients under age 65 were employed or self-employed, which is very similar to an age-matched population in the general population in Canada (www.statcan.ca/english/Pgdb/health47a.htm; March 2005). Disease activity was not related to age or disease duration, but despite this the working population in the sample decreased from 67% at BASDAI < 3 to 53% at BASDAI ≥ 7. Contrary to this, functional impairment was correlated with both age and disease duration, which contributes to the much stronger effect of functional impairment on work capacity. The proportion of patients working declined from 75% at BASDAI < 3 to 38% at BASFI ≥ 7. BASDAI, BASFI, age, and disease duration were interrelated, as expected, and the actual expected costs (and utility) for individual patients with a defined profile have to be estimated using multiple regression analysis. Table 2 presents demographics by disease severity.

Resource consumption. Hospitalization was very limited in this sample and concerned only 5 patients with a total of 12

Table 1. Patient demographics.

	All Patients	Alberta	Ontario	BC	Manitoba
No. of patients (%)	545 (100)	288 (52)	172 (33.6)	60 (9)	25 (5.3)
Male, %	64	73	55	41	70
Disease duration, yrs (mean)	22.3 (12.6)	21.0	24.3	21.2	23.5
Age, yrs (mean)	49.6 (13.3)	45.3	52.6	58.7	56.7
BASDAI (mean)	4.33 (2.19)	4.2	4.4	5.1	4.4
BASFI (mean)	3.56 (2.53)	3.2	3.7	4.3	4.6
EQ-5D	0.65 (0.23)	0.66	0.65	0.55	0.62
EuroQol visual analog scale for utility	67.2 (17.4)	66.8	69.7	59.9	67.3

Table 2. Work capacity and utility by disease severity.

	Grouped by Disease Activity (BASDAI)					
BASDAI	< 3	3–3.99	4–4.99	5–5.99	6–6.99	> 7
Distribution, %	32	12	16	18	12	12
Mean BASFI score	1.6	2.6	3.5	4.5	5.2	6.5
Mean BASDAI score	1.7	3.5	4.5	5.5	6.5	7.8
Disease duration, yrs	21.4	23.0	21.4	23.3	23.4	22.4
Age, yrs	50.0	48.9	48.4	49.6	49.4	51.2
Age < 65, %	86	88	85	83	90	91
Working (age < 65), %	67	69	66	62	54	53
	Grouped by Function (BASFI)					
BASFI	< 3	3–3.99	4–4.99	5–5.99	6–6.99	> 7
Distribution, %	47	13	11	9	7	13
Mean BASFI score	1.4	3.4	4.4	5.4	6.5	8.2
Mean BASDAI score	3.1	4.2	5.1	5.5	6.5	6.6
Disease duration, yrs	19.8	23.3	26.1	21.2	26.1	26.1
Age, yrs	46.2	51.2	54.1	49.6	51.7	55.3
Age < 65, %	92	85	84	78	87	78
Working (age < 65), %	75	67	57	53	40	38

inpatient days, establishing the mean for the sample to less than 1 day per year (0.9). Four patients underwent surgery, 2 hip replacements and 2 knee surgeries, as day cases. Based on these findings, around 3% of patients would undergo surgery every year. This is lower than what was found in the UK study (6%)[8], but may be explained by the lower age and shorter disease duration in the Canadian sample.

A total of 500 outpatient visits occurred for 37% of the sample during the 3 months, most often to the rheumatology department (38%). The visits included 339 radiographic examinations. On an annual basis, the mean number of outpatient consultations is estimated at 3.7 per patient. Community care was used by 73% of the patients, predominantly visits to general practitioners (30%), physiotherapy (18%), and massage (21%), as well as services such as home help. The mean number of physician visits or physiotherapy sessions is estimated at 15.9 per patient and year, and the mean number of other services to 4.2 per patient and year.

A large proportion of patients used chronic medication during the 3 months, essentially antiinflammatory drugs and gastroprotectants (Table 3). NSAID usage was reported by 72.3% of patients. In addition, 44% used OTC medication.

Twenty percent of patients indicated that they had retired from work due to AS (20.2%), while 98 patients had to either reduce their working time (9.5%) or change their work (8.4%). One-fifth of the patients (19%) were not in employment or were in normal retirement. Nineteen percent of patients had needed a sick leave during the past 3 months, with a mean duration of 3.6 days per month. The resulting mean annual number of sick days for the entire sample was 8 days per year, which is only somewhat higher than the average number of days lost per year, 7.5 days, due to illness or disability in the Canadian population (www.statcan.ca/english/ Pgdb/health-47a.htm; March 2005).

Costs. The mean total annual cost per patient is estimated at Cdn $9,008 (Table 4), with indirect costs representing 38%. Patients' out of pocket costs (OTC medication, investments, and informal care) represented half of direct costs and 33% of total costs. Informal care represents 25% of direct costs and 15% of total costs.

Table 3. Medication use.

	Users (% of Sample)
NSAID	36.3
COX-2 inhibitors	36.0
DMARD	11.6
Steroids	4.4
Gastroprotectants	27.2
Over the counter preparations	44.0

NSAID: nonsteroidal antiinflammatory drugs, COX: cyclooxygenase, DMARD: disease modifying antirheumatic drug.

Table 4. Mean total annual costs per patient (2003 Canadian dollars).

	Mean Cost (SD)	Percentage of Total Cost
Direct costs	5,585 (11,185)	62.0
Hospital care	1,093 (4,555)	12.1
Inpatient stays	315 (4,072)	3.5
Day care treatment	28 (452)	0.3
Outpatient attendance	750 (1,417)	8.3
Community care services	1,089 (1,937)	12.1
Medical/paramedical	835 (1,292)	9.3
Other	254 (1,368)	2.8
Medication	664 (1,706)	7.4
Prescription drugs	419 (448)	4.6
Over the counter medications	245 (1,636)	2.7
Nonmedical costs	2,739 (11,693)	30.4
Investments	1,350 (9,667)	15.0
Informal care	1,389 (6,302)	15.4
Indirect costs	3,423 (9,593)	38.0
Reduced income	972 (4,142)	10.8
Early retirement	1,800 (7,637)	20.0
Sick leave	650 (2,957)	7.2
Total cost	9,008 (17,724)	100.0

Mean costs per patient were similar in Alberta, Ontario, and Manitoba, but almost double in BC. Patients in this group used on average twice as much community services and 3 times more OTC medication, and more patients were on early retirement. The most striking difference was a 3–4 times higher need for informal care (Table 5).

Costs were not normally distributed, with a small number of patients with very high costs. The number of very severe patients with both BASFI and BASDAI $\geq$ 8 was less than 6%, but the mean annual cost increased about 6-fold for these patients compared to patients with BASFI and BASDAI $\leq$ 2 (Figure 1). Although BASFI and BASDAI are highly correlated ($r^2 = 0.73$), they influence costs to different degrees. Both are significantly correlated with costs, but functional impairment is clearly the strongest cost driver. Age is significant as well, but sex is not. Disease duration becomes nonsignificant when age is included in the regression, due to colinearity. Costs ranged from \$5,000 to \$30,000 across the BASFI (1 to 10) and from \$4,000 to \$16,500 across the BASDAI (1 to 10).

Utility. Utility was driven equally by both function and disease activity. Scores ranged from 0.79 and 0.76 for patients with BASDAI and BASFI < 3, respectively, to 0.41 for scores $\geq$ 7. Very severe patients with scores of 8 on both measures had a mean utility score as low as 0.20 (Figure 2). As expected, utility was significantly correlated with age and sex but not with disease duration when age is included in the regression model.

DISCUSSION

This is to our knowledge the first study investigating resource utilization, work capacity, and QOL of patients with AS in Canada. Our objective was to estimate costs and utilities for different levels of disease severity rather than to estimate the total burden of the disease in Canada. However, patient enrolment was entirely random, using the complete databases of patient associations or contacting all patients consulting both community-based and academic rheumatologists specializing in AS during the past 15 years. In view of this selection process, and the fact that the questionnaire was mailed, the response rate of 45% can be considered good and not expected to influence the sample. Thus, our sample may approach a true prevalence sample, despite the limited size. A larger study is under way to confirm the findings.

A number of studies have found that costs are driven by disease severity, in particular deteriorating physical function[3,8,12,13], and our results are similar. Costs increase steeply with increasing functional impairment, resulting in a 6-fold increase of costs for patients with BASFI = 10 compared to patients with BASFI = 1. When patients are grouped according to disease activity, the increase is only 4-fold. However, BASFI and BASDAI are highly correlated, and age, disease duration, and physical function are interrelated. Thus, to estimate the cost-effectiveness of treating patients with a defined profile, e.g., when using results from clinical trials, costs have to be calculated using multiple regression analysis.

Mean costs per patient are around 40% lower in Canada than in the European studies (\$9,000 compared to \$15,000), but similar to costs estimated in the United States (\$8,000). However, such comparisons are indicative at best, as they do not account for differences in the samples in terms of average disease severity, age, or sex, or in differences in the distribution of patients across the disease spectrum. Nevertheless, comparing to our study in the United Kingdom[15], it appears that direct costs were not very different, although the distribution within direct costs was not the same. Hospitalization and consultations were less frequent in Canada, while investments and informal care accounted for a higher proportion of costs compared to the UK (30% vs 16.5%). This is explained by a slightly different method in the calculation of informal care costs, where in Canada

Table 5. Mean annual cost per patient by region (2003 Canadian dollars).

	Alberta, n = 288	Ontario, n = 172	Manitoba, n = 25	BC, n = 60	All, n = 545
Direct costs	4,456	5,747	4,180	10,989	5,585
Hospital care	758	1,192	2,365	1,819	1,093
Community care	880	1,151	649	2,079	1,089
Medication	487	732	437	1,388	664
Nonmedical costs	2,331	2,670	729	5,703	2,739
Indirect costs	3,229	3,226	3,827	4,712	3,423
Total costs	7,685	8,972	8,007	15,701	9,008

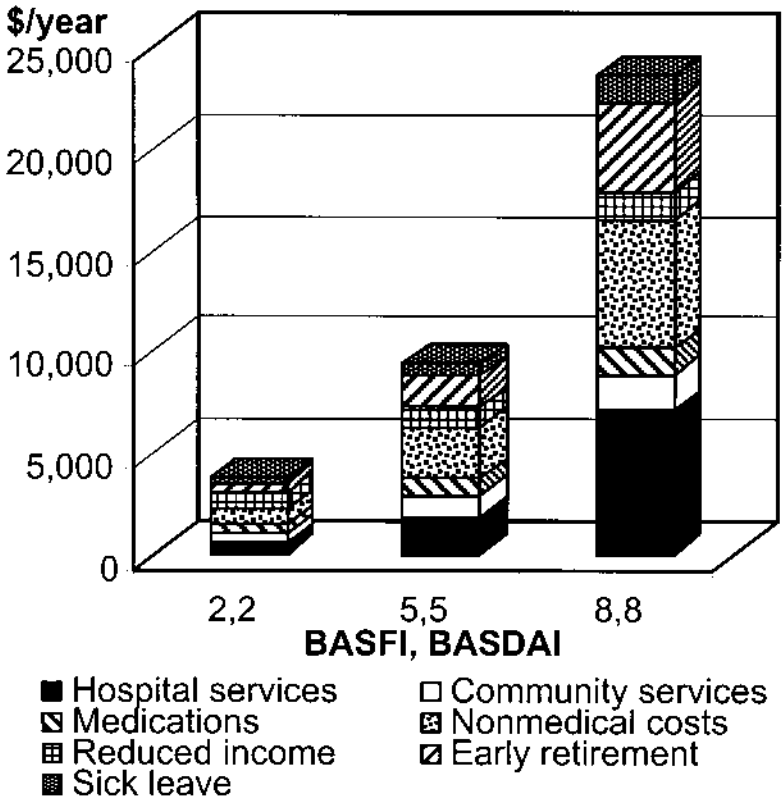

Figure 1. Mean annual costs for patients with different levels of BASDAI and BASFI. Costs are influenced by both functional impairment and disease activity, but to different degrees. Functional impairment is the strongest cost driver, although BASFI and BASDAI are highly correlated. Costs for different severity levels of AS are presented for hypothetical patients with a defined combination of BASFI and BASDAI (2,2; 5,5; 8,8).

the concept of replacement cost was used (i.e., the cost of a healthcare professional providing the care). The rationale for this was that informal care is highly concentrated in the severe disease states, where professional care would be required in the absence of informal care. This method provides generally higher costs than when the cost of leisure time is applied. The main difference between the 2 countries is in productivity losses, which were higher in the UK, accounting for 58% of total costs.

One surprising finding was the high costs for patients in British Columbia. Although this group was older and had more severe disease, and costs would therefore be expected to be higher and utility lower, these differences cannot account solely for the higher cost. One possible explanation is the size of the sample (n = 60). When excluding outliers (+2 SD), mean costs per patient were reduced to Cdn $11,468, which is more in the range with the other regions.

Mean utility scores in our study were similar to those found in the 2 European studies (0.67)[8,14], despite some differences in mean age. For instance, patients in the UK study were on average 8 years older than in Canada, and one would therefore have expected a slightly lower utility due to

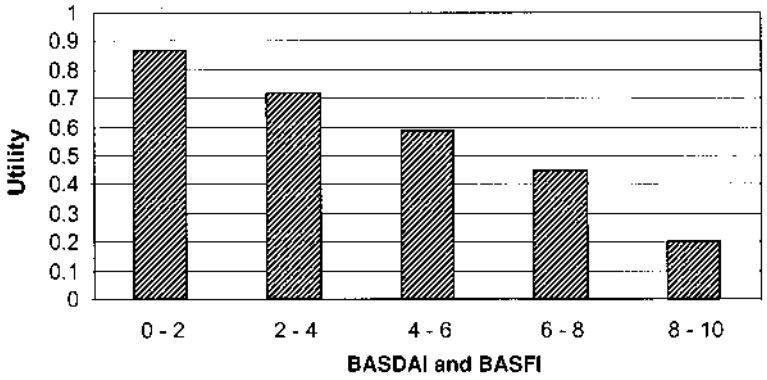

Figure 2. Utility by disease severity (BASDAI and BASFI). Utilities are influenced to a similar degree by BASDAI and BASFI, ranging from 0.865 to 0.203 for patients grouped for combinations of the 2 measures. Scores in the most severe group must be considered with caution, as they are based on fewer than 10 patients.

age. However, the mean BASDAI in the Canadian sample was higher (4.7 compared to 4.2), which appears to have compensated for the age difference. The difference cannot be explained from the dataset and might be spurious.

We have used the EQ-5D health status system developed for the United Kingdom, to ensure comparability to earlier studies in Europe. However, the tariff for North America has very recently been published and we also assessed scores using this system[25]. Scores were around 0.1 point higher at all levels of BASFI/BASDAI, with similar intervals between the levels. This is consistent with the findings of the authors of the tariff[26]. One of the objectives of our study was to estimate differences between levels of disease severity (BASDAI/BASFI) to provide data for cost-effectiveness analysis. In chronic diseases cost-effectiveness is driven by the differences in costs and utilities for different levels of disease severity rather than by absolute values. Thus, using the US tariff may lead to different absolute scores, but not to substantially different results in a cost-effectiveness analysis.

Our findings are consistent with earlier studies, although they suggest that costs more closely resemble those in the US than in Europe. Costs are driven by a number of variables, but primarily by functional status. The increase in costs and decrease in utility with worsening disease is steep, and treatments that delay progression to the more advanced disease states will avoid or delay the high costs and low quality of life associated with severe disease. The current data provide a baseline to evaluate the economic effect of such treatments.

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REFERENCES

1. Gran J, Husby G, Horvick M. Prevalence of ankylosing sponylitis in males and females in a young middle-aged population of Tromso, northern Norway. Ann Rheum Dis 1985;44:359-67.
2. 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.
3. Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. Arthritis Rheum 2002;46:223-31.
4. 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.
5. 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.
6. Ward M. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. Arthritis Care Res 1999;12:247-55.
7. Antoni C, xxx. Cooperative on QoL in Rheumatic Diseases: Results of a survey among 600 patients across 11 European countries. ACR abstract 2002.
8. 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. Rheumatology Oxford 2004; 43:1158-66.
9. Dagfinrud H, Mengshoel AM, Hagen KB, Loge JH, Kvien TK. Health status of patients with ankylosing spondylitis: a comparison with the general population. Ann Rheum Dis 2004;63:1605-10.
10. Dougados M. Treatment of spondyloarthropathies. Recent advances and prospects in 2001. Joint Bone Spine 2001;68:557-63.
11. Dougados M, Dijkmans B, Khan M, Maksymowych W, van der Linden S, Brandt J. Conventional treatments for ankylosing spondylitis. Ann Rheum Dis 2002;61 Suppl 3:iii40-50.
12. Boonen A, Severens JL. Ankylosing spondylitis: what is the cost to society, and can it be reduced? Best Pract Res Clin Rheumatol 2002;16:691-705.
13. 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.
14. Boonen A. Socioeconomic consequences of ankylosing spondylitis. Clin Exp Rheumatol 2002;20:S23-6.
15. Sieper J, Braun J. New treatment options in ankylosing spondylitis: a role for anti-TNF alpha therapy. Ann Rheum Dis 2002;61:58-61.
16. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet 2002;359:1187-93.

17. Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month randomized, placebo-controlled trial. Arthritis Rheum 2003;48:2224-33.
18. Braun J, Brandt H, Listing J, et al. Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. Ann Rheum Dis 2005;64:229-34.
19. EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199-208.
20. Dolan P, Gudex C, Kind P, Williams A. A social tariff for EuroQol: Results from a UK general population survey. Discussion paper 138. York, UK: Centre for Health Economics, University of York; 1995.
21. Calin A, Barrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
22. Garrett S, Jenkinson T, Kennedy L, 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.
23. Canadian Pharmacists Association. Compendium of pharmaceuticals and specialties. Ottawa: Canadian Pharmacists Association; 2004.
24. Régie de l'assurance maladie du Québec. Liste de médicaments. 15e édition. Québec: Régie de l'assurance maladie du Québec; 2003.
25. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43:203-20.
26. Johnson JA, Luo N, Shaw JW, Kind P, Coons SJ. Valuation of EQ-5D health states: are the United States and the United Kingdom different? Med Care 2005;43:221-8.