

# The Burden of Ankylosing Spondylitis in Spain

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## ABSTRACT

**Objective:** To investigate the burden of ankylosing spondylitis (AS) in Spain, as baseline for economic evaluation of the use of biological agents.

**Methods:** A cross-sectional retrospective observational study was performed in 601 patients with AS in Spain, using a methodology developed in studies in the United Kingdom and Canada. Patients were mailed a questionnaire asking about their health-care consumption, out-of-pocket expenses, work capacity, need for informal care during the past 3 months, as well as quality of life. Patient's current functional status and disease activity level was assessed using the Bath functional and disease activity indexes (BASFI and BASDAI).

**Results:** The mean age (median) was 47.8 (12.4) years, and the mean disease duration was 18.8 years. Eighty percent of patients were male, and slightly more than half of patients below 65 years of age were working. The mean (median) BASDAI and BASFI scores were 4.3 (2.5) and 3.8 (2.9),

respectively, and all levels of disease severity were represented. The mean (median) total annual cost per patient is estimated at €20,328 (€7920). Direct health care represented 22.8%, investments (adaptations of house and devices) and informal care 43.5%, and productivity losses 33.7%. Costs increased significantly with worsening disease, in particular diminishing physical function, covering a range between €5000 and €75,000 per patient and year. The mean (median) utility was 0.59 (0.30). Utility showed a significant inverse relation with BASFI and BASDAI, covering a range from 0.80 for patients with BASFI/BASDAI below 3 to 0.25 for patients with BASFI/BASDAI greater than 7.

**Conclusions:** As in studies in other countries, all types of costs accelerate steeply with worsening disease while utility decreases significantly, indicating the need to prevent disease progression.

**Keywords:** ankylosing spondylitis, costs, anti-TNF, utility.

## Introduction

The gradual physical impairment and inflammatory activity associated with ankylosing spondylitis (AS) have a considerable impact on health-care costs and work capacity. In particular, functional capacity has been identified as the main cost driver [1–5]. Similarly, the impact on patients' quality of life (QoL) is considerable [6,7], and utility has been shown to decrease with both increasing functional impairment and more active disease [4,5]. In studies in the United Kingdom and Canada, mean utility ranged from 0.85 for patients with BASFI (Bath Ankylosing Spondylitis Functional Index [8]) and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index [9]) below 3 to 0.20 for patients with BASFI and BASDAI of 7 and higher.

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From a socioeconomic point of view, it is thus important to use treatments that control disease activity and can prevent or slow disease progression to avoid or delay the high health-care costs and productivity losses combined with low QoL associated with severe disease. This has been shown using cost-effectiveness models in the United Kingdom and Canada [4,5,10], based on controlled and open clinical trials with infliximab, a tumor necrosis factor (TNF)- $\alpha$  inhibitor [11–15]. Cost-effectiveness estimates depend not only on the effectiveness and the price of a treatment, but also on the cost-structure underlying treatment, i.e., quantities of resources consumed and their price, as these may change with treatment. Cost-effectiveness analyses can thus not directly be transferred between different countries, as can clinical trial results.

The purpose of this analysis is therefore to estimate costs and QoL of patients with AS in Spain as a basis for cost-effectiveness analyses of new treatments for AS in a Spanish setting.

## Methods

### Data

Information was collected directly from patients using a special questionnaire developed for the earlier studies in the United Kingdom and Canada [4,5] and adapted to reflect the Spanish setting. The questionnaire asked about patients' consumption of health care and community services related to AS during the past 3 months, out-of-pocket expenses such as over-the-counter (OTC) medication, medical devices (walking aids and similar devices) and investments (e.g., changes to the car or the house), informal care needs, and work capacity (changes in work situation, short- and long-term sick leave, and early retirement).

Utility was assessed using the EQ-5D (EuroQol), a widely used generic preference-based QoL instrument [16]. The EQ-5D assesses QoL in five different domains and answers are combined into a summary score (utility) which is anchored between 1 (full health) and 0 (death). Weighting life-years with utility scores results in the quality-adjusted life-years, the most frequently used outcome measure in economic evaluations of health-care interventions. In addition, the EuroQol contains a visual analog scale (VAS) asking patients about their current health on a scale between 0 (worst) and 100 (best).

Functional status and disease activity was assessed using the BASFI and BASDAI, as these are easy to use in a mail survey and are generally included in clinical and epidemiological studies.

Fifty-one geographically spread specialized medical clinics participated in the study, led by three main centers (Hospital Universitario Reina Sofia, Cordoba; Hospital de Sabadell, Barcelona; Clinica Puerta de Hierro, Madrid). In a pilot study, the Spanish translation of the questionnaire was mailed to 30 patients in the three main centers and patients completed the questionnaire during a telephone interview to assert the ease of understanding and the accuracy of the questions. The questionnaire was modified and the final version mailed to 700 patients in April and May 2005. A special hotline was established to allow questions from patients. Completed questionnaires were returned to the Spanish Society of Rheumatology where the data were entered on an ongoing basis in a special database, and the database was locked 6 weeks after the mailing. Questionnaires were fully anonymous and it was thus not possible to verify answers or complete missing data.

### Analysis

The study was performed from the societal perspective, including all costs regardless of who pays. Individual resource quantities were multiplied with specific unit costs obtained from publicly available sources and when necessary inflated to 2005. The majority of unit

costs (inpatient and outpatient care) were taken from the SOIKOS database (Base de Datos de Costes Sanitarios, SOIKOS). Prescription drug costs were calculated based on the average daily dose actually consumed (IMS Spain Pharmaceutical Sales Report 2005), using public drug prices (Catalogo de Especialidades Farmacéuticas, CEF), while OTC medication was based on patients' indications of total costs. Services such as home help were valued using public costs (Boletín Oficial del Estado Español, March 21, 2005). Informal care was considered a direct cost and estimated using the replacement method, i.e., applying to cost of a professional to perform the service (other methods to estimate informal care costs are productivity losses of the carer or disposable income per hour of care.) Out-of-pocket expenses were included as indicated by patients, as particularly for, e.g., investments, it is impossible to estimate a standard unit cost. Loss of work capacity included sick leave, reductions in working time because of AS, and early retirement, and was estimated using the human capital approach where the cost of lost production is valued with the cost of labor. Thus, a sex-specific mean hourly wage, including employers' contributions, was applied (Agencia Tributaria, Seguridad Social, Secretaria de estado, and Instituto Nacional de Estadística).

Three-month resource consumption was annualized by multiplication by 4, under the assumption that any one 3-month period is representative of other quarters, with a similar proportion of patients using a given resource. Results are presented as the mean and median annual cost per patient. Nevertheless, as costs are highly correlated with both physical function and disease activity, mean costs are dependent on the sample included in the study. We therefore also present the costs for given combinations of disease severity (BASFI and BASDAI).

Utilities were analyzed using the health status tariff developed with the original EQ-5D instrument in the United Kingdom [17], on the one hand to obtain data that can be compared to the studies in the United Kingdom and Canada, on the other hand because the UK tariff is the only one in Europe to have been developed using decision analytic tools (time trade off) with the general population.

## Results

### Patient Demographics and Work Capacity

In total 601 completed questionnaires were received, establishing a response rate of 85.7%. No answer 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 the sample was 47.8 (range 18–84) years, and 91% of the patients were below 65 years old. Eighty percent of the respondents were male. The mean disease duration was 18.8 years (SD 10.9), and

**Table 1** Sample demographics

	Mean, %	SD
No of patients	601	
Male	80%	
Age (year)	47.8	12.36
Patients <65 years	91%	
Patients working (patients <65 years)	53%	
Disease duration (year)	18.8	10.9
BASDAI	4.3	2.45
BASFI	3.8	2.85
Flares in the past 3 months	52%	
Utility (EQ-5D, range 0–1)	0.59	0.30
EuroQol VAS (range 0–100)	60.5	20.5

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; VAS, visual analog scale.

the Mean BASDAI and BASFI scores were 4.3 (SD 2.45) and 3.8 (SD 2.85), respectively. Median scores were 4.4 and 3.4, and the full range of the two scales was covered. Mean utility was 0.59 (SD 0.30), corresponding to the scores for patients with a BASDAI ranging between 4 and 5, or a BASFI ranging between 3 and 6. The mean score on the EuroQol VAS was 60.5 (SD 20.5).

The majority of patients in the sample had relatively mild disease. Close to half of the patients (46%) had no or only minimal functional impairment (BASFI < 3), and 45% had a BASDAI score below 4. More than 90% of patients were below 65 years of age, and of these 53% were working. This is, however, lower than the estimated workforce participation of 69% for a population with a similar sex distribution (the 2004 employment rates: 74% for men, 48% for women, <http://www1.oecd.org>), indicating the impact of the disease on employment. In the early stages of the disease, the effect is limited and 63% of patients are working at BASFI/BASDAI below 3. At this stage, the effect of inflammation is as expected stronger than functional decline, with 70% of patients working

when only BASFI is taken into account. The situation reverses in late disease, where only 24% of patients with BASFI greater than 7 work, compared to 37% when only BASDAI is considered. Thus, the loss of work capacity with advancing disease, considering also that age and disease progression are linked, can be estimated at around 30%, and the total effect in our sample at around 15%. Almost a quarter of patients in the sample (24.5%) had had to stop working because of the disease, while 13% had reduced their working hours and 19% had changed their job as a consequence of AS.

BASDAI and BASFI, as well as age and disease duration were all significantly correlated (colinearity), as illustrated in Table 2, and the actual expected costs and utility for individual patients with a defined profile are therefore estimated using multiple regression analysis.

### Resource Consumption

Details on resource consumption are presented in Table 3. Hospital admission was required for 23 patients (4%), establishing the mean for the sample to 1.7 days per year. Half of these admissions (12) were for surgery while a further seven patients underwent eight ambulatory interventions. Among these, five patients had hip replacement, two had neck surgery, and one had knee surgery, with the remainder having other unspecified interventions. Assuming that the 3 months of data collection are representative for all quarters, an estimated 13% of patients would undergo any type of surgery per year, and major interventions would happen in 5% of patients. This is comparable to what was seen in similar studies in the United Kingdom (6%) and Canada (3%) [4,5].

A total of 992 outpatient visits to specialists occurred for 76% of the sample during the 3 months, most often to the rheumatology department (54%).

**Table 2** Relationships between disease severity (BASDAI, BASFI), disease duration, age, work capacity, and utility

	<3	3–3.99	4–4.99	5–5.99	6–6.99	>7
Disease severity according to BASDAI						
Distribution of sample (%)	33	12	13	13	15	15
BASDAI (mean)	1.5	3.5	4.5	5.4	6.4	8.1
BASFI (mean)	1.4	3.1	3.8	4.8	5.5	7.1
Age (year)	44.9	46.9	50.1	48.1	49.9	50.7
Disease duration (mean)	16.3	18.6	21.6	19.8	19.0	21.4
Age <65 years (%)	89	95	88	95	92	90
Working (age <65 years) (%)	63	66	47	52	45	37
Disease severity according to BASFI						
Distribution of sample (%)	46	10	9	9	9	17
BASFI (mean)	1.2	3.4	4.5	5.4	6.5	8.4
BASDAI (mean)	2.7	4.5	4.9	4.9	6.1	7.1
Age (year)	44.8	50.1	44.7	51.7	49.2	53.5
Disease duration (mean)	16.0	18.3	16.8	23.8	22.5	23.4
Age <65 years (%)	92	86	98	90	94	85
Working (age <65 years) (%)	70	46	57	35	43	24

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.

**Table 3** Resource consumption

Resource	Proportion of patients in the sample using the resource (%)	Mean quantity per patient in the sample per year
Hospital care		
Inpatient days	4	1.7
Outpatient visits	76	7.5
Tests	76	7.1
Hospital drugs	27.1	n/a
Community care		
General practitioner visits	76	9.6
Paramedical and other services	80	6.9
Drugs	96	n/a
NSAIDs	72	n/a
Cox2 inhibitors	3	n/a
DMARDs	24	n/a
Steroids	5	n/a
Gastroprotectants	47	n/a
Investments (appliances, changes to house and care)	9	n/a
Informal care (hours of help per year)	26.6	93.6

DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.

The visits included 494 x-ray examinations, 23 bone scans, 23 magnetic resonance imaging scans, 26 CT scans, 21 densitometries, and 11 gastroscopies, as well as a total of 939 blood and urine tests. On an annual basis, the mean number of outpatient consultations is estimated at 7.5 per patient. This is considerably more than what had been found in the United Kingdom (2.2) and in Canada (3.7) [4,5], indicating strong differences in patient management. Visits to general practitioners (GPs) and paramedical professionals were estimated at 18.7 per patient per year. Most of these visits were to GPs (9.5/patient/year) and physiotherapists or massage specialists (5.8/patient/year).

Almost all patients (96%) used chronic medication, most frequently nonsteroidal anti-inflammatory drugs (NSAIDs, predominantly indomethacin, paracetamol, naproxen, and ibuprofen), disease-modifying antirheumatic drugs (predominantly sulfasalazine and methotrexate), and gastroprotectants (mostly proton pump inhibitors); only 12.4% of patients used OTC medication. Twenty-six percent of the sample used infliximab, the only biological available in Spain at the time of the study, with an infusion given on average every 7 weeks.

Informal care was provided by families and friends to 27% of patients, for an average of 1 h per day, or 15 h on average per year for all patients in the sample. As expected, informal care was concentrated in patients with advanced disease. Only 8% of patients at BASFI/BASDAI below 3 used informal care, for an average of 16 h per week, while this proportion increased to 83% of patients and 47 h per week for patients at BASDAI/BASFI greater than 7.

**Costs**

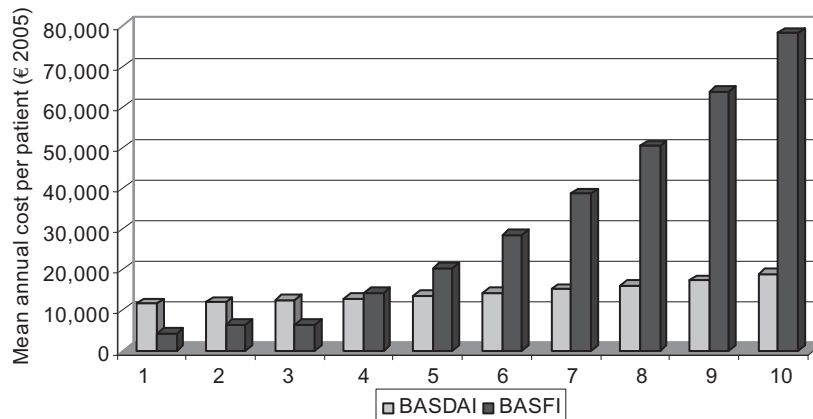
The mean total annual cost per patient in the sample is estimated at €20,328 (SD 39,638), with indirect costs

representing 33.7% (Table 4). Patients' out-of-pocket costs (OTC medication, investments, and informal care) represented the largest burden, estimated at 43.5%, driven by informal care (34% of total costs). Despite the relatively frequent use of a biological drug, medication represents only 10.6% of total costs. Mean costs are representative for a patient with a BASDAI/BASFI of around 4, but the large standard deviation indicates both the variability and the significant relationship with disease severity, as shown in Figure 1. BASFI and BASDAI are highly correlated ( $r^2 = 0.73$ ), but they influence costs to a different degree. Although inflammation appears to have a rather steady but limited impact on costs, the cost increase with

**Table 4** Total mean annual cost per patient (€ 2005)

	Mean cost	SD	% of total cost
Total cost (N = 601)	20,328	39,638	
Direct cost	13,485	36,066	66.3
Hospital care	1,697	7,358	8.4
Inpatient stays	1,033	7,200	5.1
Outpatient attendance and tests	664	915	3.3
Community care	780	1,986	3.8
Medical/paramedical services	427	1,096	2.1
Other community services	353	1,440	1.7
Medication	2,164	3,666	10.6
Hospital drugs	1,963	3,661	9.7
Prescription drugs	170	234	0.8
OTC medications	30	301	0.1
Nonmedical costs	8,845	33,141	43.5
Investments	1,923	23,455	9.5
Informal care	6,921	23,589	34.0
Indirect costs	6,843	9,890	33.7
Reduced income	258	1,526	1.3
Early retirement	5,935	9,717	29.2
Sick leave	649	3,188	3.2

Costs are presented from the societal perspective, including all costs regardless of who pays. The mean cost for a patient in the sample corresponds to costs for a patient with a BASFI/BASDAI around 4. OTC, over-the-counter.



**Figure 1** Mean costs per patient in relation to disease severity. Costs are calculated using regression analysis where either Bath Ankylosing Spondylitis Functional Index (BASFI) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is kept constant at the mean score of the sample, to investigate the effect of each of these measures on cost. Functional decline (BASFI) exerts a much stronger effect on costs than the severity of disease activity (BASDAI). Costs increase from €4260 at BASFI of 1 to €78,300 at BASFI of 10, while they increase from €11,600 at BASDAI of 1 to €18,900 at BASDAI of 10. Nevertheless, the two measures are highly significantly correlate ( $r^2 = 0.73$ ) and the costs can thus not be calculated independently for these variables. The surprisingly high costs at the low BASDAI scores are a result of the considerable number of patients in the sample treated with infliximab who thus reach low disease activity levels (see Figure 3).

advancing functional disability is very steep and reaches more than €75,000 for patients with BASFI of 10. All types of expenses increase, but the bulk is due to informal care and early retirement.

**Utility**

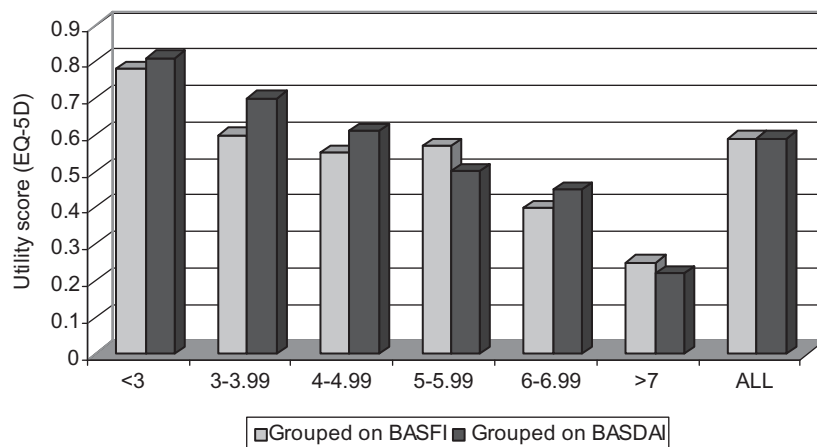
Mean utility in the sample was 0.59 (SD 0.30). This compares to an expected score in the normal male population of 0.89 for the age group of 40 to 49 years and 0.80 for the age group of 50 to 59 years. The mean EuroQol VAS score was 60.5 (SD 20.5), compared to an expected 95.0 in the age group of 40 to 49 years and 85.1 in the age group of 50 to 59 years in Spain [18].

Utility was driven equally by both function and disease activity, and decreased steadily from around 0.80 in early disease to 0.25 for patients with scores of 7 and above (Fig. 2). As expected, utility was signifi-

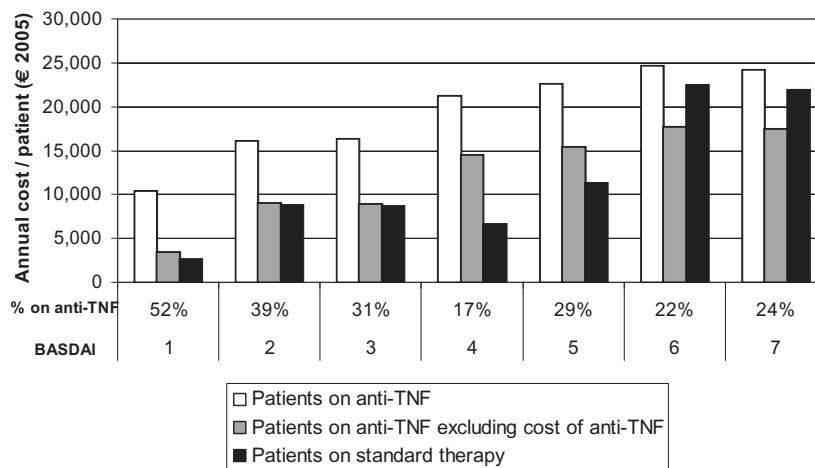
cantly correlated with age and sex but not with disease duration when age is included in the regression model.

**Discussion**

As more effective but also more expensive treatments are introduced, cost-effectiveness analyses have become an important tool to relate the investment to the value of the health improvements. In chronic disease, such studies require data on the disease and its progression as well as its effect on QoL, the effectiveness of treatment, and current resource consumption related to the disease. Although epidemiological and clinical data are transferable between settings in most cases, resource consumption and hence costs are not. Different countries have different organizations of care and medical traditions. Both the availability and the



**Figure 2** Utility scores related to disease severity. Utilities represent quality-of-life weights calculated on a scale between 0 = death and 1 = full health. The effect of the disease, both functional decline and disease activity, is evident in the sharp decline of scores. Although utility scores are correlated with age, the mean age of patients at Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 10 is only about 10 years higher than the age of patients with very mild disease. Thus, about 80% of the decline is due to the disease.



**Figure 3** Costs for patients with naturally low disease activity (standard therapy) or low Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) due to anti-TNF treatment. Overall in the sample, costs at the same level of BASDAI are not significantly different for patients on anti-TNF therapy and those on standard therapy, when the cost of anti-TNF therapy is excluded from the regression analysis. When looking at costs at individual levels of BASDAI, it has to be borne in mind that the number of patients treated in some of these groups are too small (around 20 or less in most groups above BASDAI of 3, and, e.g., only 13 patients at BASDAI of 4) to draw any conclusions. Nevertheless, it would appear that patients at levels 4 and 5 on anti-TNF therapy are possibly more closely managed to reduce disease activity, or may have more impairment, which would select them for anti-TNF therapy. Interestingly, at higher levels of disease activity, the cost of anti-TNF therapy appears to be almost entirely offset through savings in other costs. This is illustrated best at the lowest cost levels of BASDAI.

cost of resources vary, and country-specific observational studies are needed to ensure that economic evaluations are relevant and meaningful. The current cross-sectional study in a large sample of Spanish patients not only provides solid data for economic evaluation in Spain, but also contributes to our general knowledge about consumption of patients with AS, and can be compared to our earlier studies using a similar methodology in the United Kingdom and Canada.

All our data were collected retrospectively directly from patients with a validated but fully anonymous questionnaire. Earlier studies in AS [4,5] and other fields [19] have shown that this mode of data collection, when relevant recall periods for each resource are used, provides not only accurate, but also the most detailed information on costs. At the same time, it allows to collect QoL data that relate to both current disease status and resource consumption. This advantage outweighs any potential issue of recall bias, or of the need to annualize costs from monthly or quarterly costs.

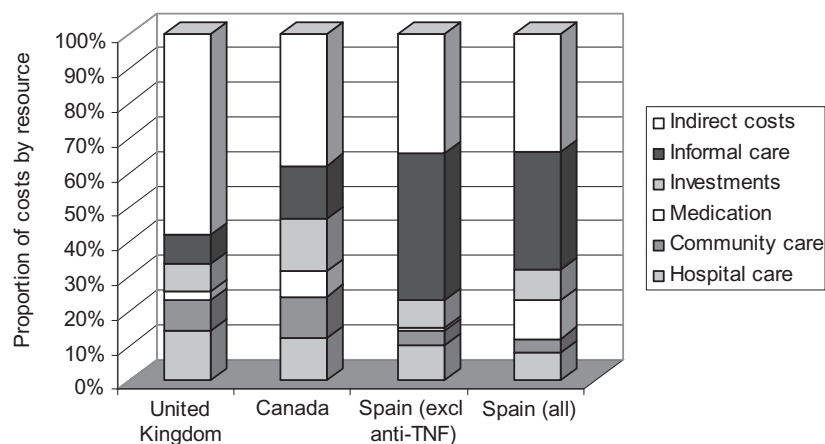
The results of this study in Spain confirm again the overall findings of the earlier studies. The majority of costs are outside the formal health-care sector and relate to informal care by family and loss of work capacity. Costs are primarily driven by functional decline, while the severity of disease activity appears to have a limited impact on consumption. This result is more pronounced in Spain than in our earlier studies, and can be explained by the fact that around a quarter of patients in the sample were treated with an anti-

TNF drug (infliximab). Consequently, these patients' disease activity was in the lower range, while their costs were relatively high, as shown in Figure 3.

This is the first observational study that includes patients treated with biological drugs, and it is interesting to note that at a given level of disease activity, there is no significant difference in costs other than drug costs and related infusion visits between patients treated with infliximab or not. Patients for our study were recruited via specialized clinics, and it must therefore be expected that the proportion of patients on infliximab in our study does not fully reflect the usage of biological drugs in Spain at the time. Indeed, among the first 1385 patients included in the Spanish national registry, only 16.6% use biological drugs [20]. Nevertheless, as now further anti-TNF drugs have been introduced since, it is well possible that the findings in our study reflect current usage more closely.

Cost comparisons between studies performed in different countries have to be done with utmost care, as consumption is influenced by a number of factors: disease severity in the sample, health-care provision, unit costs of the resources, timing of the study and, not the least, family tradition. A good example of this issue is our finding regarding the considerable differences in the number of outpatient visits in Spain, Canada, and the United Kingdom, with, however, a relatively small difference in costs due to different unit prices for a visit.

A comparison of the Spanish results to our earlier studies in Canada and the United Kingdom is, however, interesting in several other aspects (Fig. 4).



**Figure 4** Costs in Spain. Costs in Spain were found to be higher than in the United Kingdom and Canada, predominantly because of the more intensive use of informal care by Spanish patients.

The major difference between the Spanish results and the other studies is the inclusion of patients treated with an anti-TNF agent due to a difference in the timing. Nevertheless, even if we exclude this treatment, costs in Spain are substantially higher; almost twice those in the United Kingdom and nearly three times those in Canada. The difference is mainly due to a much more intensive use of family support by Spanish patients, with informal care representing 34% of total costs in the sample (42% if patients on anti-TNF agents are excluded), compared to 8.5% in the United Kingdom and 15.4% in Canada. This is not explained by a difference in disease severity. BASDAI was 4.2 to 4.3 in all three samples, and function was worse in the UK sample where the mean age and disease duration were also higher (BASFI 4.4 compared to 3.6 in Canada and 3.8 in Spain). Rather, one could hypothesize that the concept of informal care in the Mediterranean area may be different from Anglo-Saxon countries. As fewer women are in the work force and family ties remain closer, family help is more readily available to a group of mainly male patients. This is a weakness in our data collection where, in order not to lengthen an already extensive questionnaire, details on what type of help patients received were not included and further research into this may be warranted. We found similar results in a recent multinational study in Europe, where informal care was more intensely used in Southern Europe compared to Northern Europe [19].

When comparing only health-care costs (adjusted for different timing), the differences become much smaller: €2700 in Spain, €2600 in the United Kingdom, and €1800 in Canada (where patients had the lowest physical impairment). These costs are less sensitive to progressing disease, where the loss of work capacity and the need for informal care become more dominant, as is generally the case in chronic progressing and disabling diseases. Productivity losses are high in AS, more than one-third of total costs, as the disease

is more frequent in men who in general have a higher workforce participation and higher income. The estimates of work capacity are based on 523 patients only, as answers were missing or were incomplete for 78 patients (13%). Most of these patients (71) were below 65 years old, and one could assume that the absence of an answer indicates that they are not working or are home workers. In this case, the proportion of patients in the work force would be lower (47% of patients below 65 years rather than 53%) and possibly indicate an even stronger effect of the disease on work capacity than estimated in our study.

The cross-sectional and uncontrolled nature of our observational study does not allow for analysis of differences in outcome between patients on anti-TNF treatments and those on standard NSAIDs. QoL is driven by disease activity and functional disability, and patients at the same levels of BASDAI/BASFI will thus have a similar QoL regardless of treatment. Outcome will have to be measured over the long-term, as there are early indications that the reduction of inflammation will reduce structural damage and thus improve the long-term prognosis [13,20]. Nevertheless, until such follow-up data become available, long-term outcome has to be modeled, based on clinical data.

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