Direct costs in patients with chronic inflammatory arthropathies on biological therapy: a real-world data study

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Abstract

Objective

The aim of the study was to assess the direct costs for the Spanish Health System of patients with chronic inflammatory arthropathies treated with biological therapies in daily clinical practice and to establish possible factors associated with lower costs.

Methods

A descriptive, observational and retrospective study was conducted. Patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis who started a biological therapy between 1 January 2009 and 31 December 2016 were included. Variables related to socioeconomic status, disease and biological therapy were included. The annual cost of biological treatment and other direct medical costs were calculated for each disease. The analysis of costs was based on the National Health Service perspective. The time horizon comprised the 8-year long study period.

Results

A total of 422 biological therapy lines were analysed. The annual biological therapy cost per patient was €12,494±3,865 for rheumatoid arthritis, €11,248±2,763 for ankylosing spondylitis and €12,263±35,155 for psoriatic arthritis (p=0.008). The cost of biological therapies entailed about 80% of the total cost of these diseases. Hospital admission was a factor which contributed to an increasing cost in all these conditions. A longer duration of the biological therapy was associated with lower cost in all the diseases.

Conclusion

The cost of ankylosing spondylitis is lower than that of rheumatoid arthritis and psoriatic arthritis. The biological therapy is the factor with the highest impact on the overall cost of these diseases. Preventing hospital admissions and a higher persistence to the biological therapy can contribute to lower costs for the system.

Key words

cost analyses, health care costs, drug costs, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis

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Introduction

Chronic inflammatory arthropathies (CIA) such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) have been traditionally treated with non-steroidal anti-inflammatory drugs or glucocorticoids (GC). Synthetic disease-modifying anti-rheumatic drugs (DMARDs), most notably, methotrexate (MTX) are used when patients do not respond to those therapies. Such drugs continue to be the basis of all CIA treatments together with non-pharmacological measures such as moderate exercise, patient education or psychological support. However, the introduction of biological therapies (BT) has contributed to improve the prognosis of these diseases and the quality of life of patients (1). On the other hand, these therapies have resulted in a higher financial burden for health systems due to their cost and the inherent chronicity of these diseases (2-7).

There is no conclusive data to determine whether the severity of the disease, age and sex of patients or their comorbidities can lead to higher costs in patients with RA (8-11), AS (12-13) or PsA (14-19). In addition, evidence suggests that the real cost of BT in daily practice differs from their stipulated manufacturer price (20-27).

Given the current lack of certainty in relation to the real costs of CIA, related to both hospital resource use and to the cost of BT in clinical practice, a real-world analysis could contribute to the implementation of measures which ensure a more efficient use of resources on CIA patients.

The objective of this study was to assess the direct costs for the Spanish Health System of CIA patients on BT treatment in daily clinical practice and to establish possible factors associated with lower costs.

Material and methods

This is a descriptive, observational and retrospective study covering an 8-year period (from January 2009 to December 2016). Data on the diseases and drug use were gathered from the patients' electronic clinical records in order to obtain an accurate representation of the pattern of routine clinical practice.

Inclusion criteria were the following: a) adult patients diagnosed with RA (according to the 1987 Rheumatoid Arthritis Classification) (28), AS according to the New York Modified criteria/The Assessment of Spondyloarthritis International Society (ASAS) Classification Criteria for Axial Spondyloarthritis (29-30) and PsA according to the Classification Criteria for Psoriatic Arthritis (31); b) patient follow-up by the Rheumatology Department; c) start of BT with infliximab, etanercept, adalimumab, certolizumab, golimumab, abatacept, tocilizumab or ustekinumab during the study period and d) BT duration of at least 180 days.

Exclusion criteria were the following: a) patients taking part in any clinical study either during the period of this study or three months prior to its start and b) non-compliance with the inclusion criteria.

Definition of variables

At the start of BT the following non-BT related variables were taken into account: demographic (age, sex), smoking habits, employment status, clinical such as diagnosis, disease duration and comorbidities (analysed and ranked according to the Charlson Index) (32) and analytical parameters: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and haemoglobin (Hb).

In relation to BT, initial dose regimen and variations throughout treatment, BT administration place (day hospital or outside of hospital) and line number as well as concomitant treatments at the start of the BT (MTX, leflunomide and GC) were recorded. Concomitant treatment with psychoactive drugs at the start of BT was taken into account (NO5B, N05C, N06A, N06B, N06C and N06D, according to the Anatomical Therapeutic Chemical Classification System) (33).

The analysis of costs was based on the National Health Service perspective and only direct costs related to the study diseases were considered. The time horizon comprised the 8-year study period.

The total sum of the costs was divided by treatment duration and then multi-

Table I. General characteristics of the study population per disease: rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

	RA (n=215)	AS (n=107)	PsA (n=100)	*p* -value
Age (years); mean±SD	54.0 ± 13.8	43.1 ± 12.5	47.4 ± 12.1	< 0.001
Women, n (%)	150 (69.9)	24 (22.4)	53 (53.0)	
Men, n (%)	65 (30.2)	83 (77.6)	47 (47.0)	<0.001
Disease duration in years				
Median (IR)	6.3 (0-35)	4.4 (0-33)	5.1 (0-46)	0.068
Haemoglobin (mg/dL)	n=208	n=103	n=94	
Mean±SD	13.0 ± 1.5	14.1 ± 1.5	13.2 ± 1.6	<0.001
CRP (mg/L); median (IR)	n = 199	n = 104	n=87	
	9.8 (3.4-23.0)	7.2 (3.0-17.0)	5.0 (2.0-15.2)	0.018
ESR (mm/h); median (IR)	n=201	n=102	n=92	
	28.0 (14.0-50.5)	14.5 (8.0-32.0)	20.5 (9.3-40.5)	<0.001
Employment status; n (%)	n=182	n=87	n = 79	
Unemployed, on sick leave or student	30 (16.5)	29 (33.3)	20 (25.3)	
Pensioner	70 (38.5)	14 (16.1)	17 (21.5)	<0.001
Employed or Homemaker	82 (45.1)	44 (50.6)	42 (53.2)	
Comorbidities (Charlson Index); n (%)	n=215	n=107	n = 100	
Between 0-3	60 (27.9)	51 (48.1)	43 (43.0)	
Between 4-9	109 (50.7)	44 (41.5)	48 (48.0)	<0.001
>10	46 (21.4)	11 (10.4)	9 (9.0)	
Smoking habit [¥]; n (%)	n=147	n=79	n = 57	
Yes	37 (25.2)	29 (36.7)	20 (35.1)	0.137
No	110 (55.8)	50 (25.4)	37	
On any psychoactive drug[‖]; n (%)	n=215	n=106	n = 98	
Yes	66 (30.7)	31 (29.2)	43 (43.9)	0.042
No	149 (69.3)	75 (70.8)	55 (56.1)	
MTX treatment at the start of BT; n (%)	n=212	n=67	n = 100	
Yes	111 (52.4)	6 (9.0)	49 (49.0)	0.119
No	101 (47.6)	61 (91.0)	51 (51.0)	
LFN treatment at the start of BT; n (%)	n=212	n=65	n = 91	
Yes	21 (9.9)	1 (1.5)	7 (24.1)	0.084
No	191 (56.2)	64 (98.5)	91 (26.3)	
GC treatment at the start of BT; n (%)	n=209	n=105	n=96	
Yes	173 (82.8)	17 (16.2)	56 (58.3)	<0.001
No	36 (17.2)	88 (83.8)	40 (41.7)	
Biological therapy, n (%)				
Adalimumab	71 (33.0)	56 (52.3)	53 (53.0)	
Etanercept	57 (26.5)	37 (34.6)	26 (26.0)	
Infliximab	6 (2.8)	1 (0.9)	4 (4.0)	
Golimumab	14 (6.6)	12 (11.2)	9 (9.0)	
Certolizumab	16 (7.4)	1 (0.9)	3 (3.0)	
Abatacept	29 (13.5)	0 (0.0	0 (0.0))	
Tocilizumab	22 (10.2)	0 (0.0)	3 (3.0)	
Ustekinumab	0 (0.0)	0 (0.0)	2 (2.0)	

To calculate the percentages, the number of events was divided by the number of analysed patients in each disease.
AS: ankylosing spondylitis; BT: biological therapy; GC: glucocorticoid; IR: interquartile range; LFN: leflunomide; MTX: methotrexate; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SD: standard deviation.
[¥]Active smoker at the start of biological therapy.
[‖] Patients on treatment with a psychoactive drug at the start of biological therapy.

plied by 365 (days) in order to allow for comparisons among diseases.

The analysis of hospital resource costs (non-pharmacological costs) was based on the following criteria: hospital admissions, visits to the Emergency Service, consultations at the Rheumatology Department, imaging diagnosis tests, consultations at other speciality departments, visits to the Outpatient Hospital Pharmacy and appointments at the day hospital for the administration of intravenous BT. The Decree of the Autonomous Community of Galicia published in 2012 was used in order to calculate resources costs (34).

Regarding pharmacological costs, only the BT cost was taken into account. The dosage and cost per patient were first established and then the average annual value per disease was calculated. To that end, the unit wholesale acquisition costs for 2016 were considered. Taxes and discounts were not considered. Costs related to the intravenous administration of the BT drugs (at the day hospital) were regarded as non-pharmacological.

Table II. Healthcare resources used by study patients per disease.

		Mean (SD)	Median (IR)	*p*-value
Visits to a Secondary care physician (no rheumatologist) per BT year	RA	3.37 (3.58)	2.52 (0-20.54)	0.457
	AS	3.40 (3.86)	2.32 (0-17.52)	
	PsA	4.91 (7.55)	2.05 (0-41.91)	
Total number of visits to Rheumatology Department per BT year	RA	2.53 (1.58)	2.37 (0-8.99)	0.004
	AS	2.23 (1.32)	1.99 (0-8.18)	
	PsA	2.73 (1.63)	2.45 (0.84-10.81)	
Urgent visits to Rheumatology Department per BT year	RA	0.80 (1.03)	0.51 (0-5.26)	0.275
	AS	0.63 (0.81)	0.37 (0-4.35)	
	PsA	0.80 (1.00)	0.45 (0-6.76)	
Visits to Outpatient Hospital Pharmacy per BT year	RA	7.22 (3.80)	8.27 (0-14.34)	0.831
	AS	8.09 (2.26)	8.14 (0-14.95)	
	PsA	7.88 (2.92)	8.27 (0-14.87)	
Visits to day hospital per BT year	RA	1.83 (4.25)	0.00 (0-13.63)	<0.001
	AS	0.05 (0.54)	0.00 (0-5.56)	
	PsA	0.66 (2.54)	0.00 (0-13.50)	
Visits to Rehabilitation Department per BT year	RA	0.13 (0.58)	0.00 (0-6.27)	0.282
	AS	0.22 (0.84)	0.00 (0-6.23)	
	PsA	0.23 (0.81)	0.00 (0-6.76)	
Hospital admissions per BT year	RA	0.20 (0.41)	0.00 (0-2.87)	0.015
	AS	0.09 (0.24)	0.00 (0-1.33)	
	PsA	0.11 (0.42)	0.00 (0-3.71)	
Visits to Emergency Department per BT year	RA	0.33 (0.57)	0.00 (0-3.87)	0.887
	AS	0.36 (0.78)	0.00 (0-5.84)	
	PsA	0.31 (0.60)	0.00 (0-3.71)	
MRI scans per BT year	RA	0.12 (0.32)	0.00 (0-1.84)	0.008
	AS	0.16 (0.32)	0.00 (0-1.71)	
	PsA	0.21 (0.37)	0.00 (0-1.87)	
Nuclear medicine scans per BT year	RA	0.05 (0.25)	0.00 (0-2.48)	0.839
	AS	0.08 (0.62)	0.00 (0-6.23)	
	PsA	0.07 (0.36)	0.00 (0-2.52)	
Radiological tests per BT year	RA	1.86 (2.25)	1.29 (0-14.37)	0.002
	AS	0.99 (1.16)	0.70 (0-7.47)	
	PsA	1.73 (2.62)	1.07 (0-22.23)	

AS: ankylosing spondylitis (n=107); BT: biological therapy; IR: interquartile range; MRI: magnetic resonance imaging; PsA: psoriatic arthritis (n=100); RA: rheumatoid arthritis (n=215); SD: standard deviation.

Cost in relation to pharmacy preparation of BT drugs was not taken into account.

In order to adjust costs obtained from different time periods (hospital resource costs from 2012 and pharmacologic cost from 2016), a rate of 1.2% was added to the hospital resource costs corresponding to the inflation rate for the 2012–2016 period.

Statistics

A descriptive analysis of the study sample was carried out. Quantitative variables were expressed as mean ± standard deviation (SD) for normal distribution and median and interquartile range (IR) for non-normal distribution. Categorical variables were expressed as absolute and relative frequencies. Differences between diseases were compared by ANOVA or Kruskall-Wallis for quantitative variables and chi-square test for qualitative variables. The sample was divided per disease in order to establish the impact of every variable studied on each condition. To compare the overall cost with a quantitative variable, the Spearman correlation coefficient was used. Student' t- and ANOVA parametric test or Mann-Whitney or Kruskall-Wallis non-parametric test were used to compare the overall cost with qualitative variables. At a later stage, and in order to assess the possible factors affecting the cost of the diseases, simple and multiple linear regression analysis were carried out. In the multiple regression analysis, those variables with a p-value <0.1 in the simple regression analysis were included as independent variables.

The accepted significance level for all hypothesis contrasts was 0.05. For the statistical analysis the SPSS programme v. 19 was used.

Ethics

The study complied with the December 13 15/1999 Law on Personal Data Protection. All data were used for the sole purpose of this study and remain confidential and anonymous. The study was approved by the Healthcare Research Ethics Committee of Galicia, under code 2014/187.

Table III. Total costs per disease. Descriptive analysis.

	RA		AS		PsA	
	Total cost (euros) mean ± SD	*p*-value	Total cost (euros) mean ± SD	*p*-value	Total cost (euros) mean ± SD	*p*-value
Women	12,468 ± 3,942	0.735	12,123 ± 2,553	0.137	12,702 ± 5,262	0.371
Men	12,644 ± 3,810		11,016 ± 2,800		11,813 ± 2,619	
Employment status:						
Unemployed/on sick leave or student	12,341 ± 2,973		11,623 ± 3,078		11,587 ± 2,257	
Pensioner	13,214 ± 4,911	0.104	11,816 ± 2,125	0.930	12,736 ± 6,007	0.890
Employed or homemaker	11,914 ± 2,725		11,108 ± 2,914		12,360 ± 4,876	
Comorbidities (Charlson Index)						
Between 0-3	11.598 ± 2,379		10,563 ± 2,808		11,290 ± 1,730	
Between 4-9	12,312 ± 3,878	0.008	11,665 ± 2,549	0.071	12,521 ± 4,846	0.034
≥10	14,218 ± 4,944		11,570 ± 2,957		15,767 ± 6,995	
Smoking habit [¥]						
Yes	12,014 ± 3,632	0.143	11,610 ± 3,545	0.069	12,237 ± 3,349	0.536
No	13,145 ± 4,334		11,733 ± 2,174		12,857 ± 3,746	
Psychoactive drug intake [‖]						
Yes	12,819 ± 3,484	0.285	11,485 ± 2,760	0.705	13,137 ± 5,301	0.042
No	12,389 ± 4,068		11,150 ± 2,804		11,672 ± 3,158	
Type of BT						
Anti-TNF-α group	11,836 ± 3,238	<0.001	11,264 ± 2,774		12,075 ± 4,192	0.003
Non anti-TNF-α group	14,755 ± 4,906		No patients		16,255 ± 3,175	
Number of BT lines						
First BT line	11,789 ± 2,617	0.004	11,313 ± 2,866	0.900	12,111 ± 4,709	0.233
Second or successive BT lines	13,411 ± 4,900		11,168 ± 2,619		12,567 ± 3,359	
Administration of BT						
Outside of hospital	11,820 ± 3,216	<0.001	11,144 ± 2,491	0.019	12,046 ± 4,211	0.007
Day hospital	16,008 ± 5,014		24,020 ± 0		15,439 ± 3,377	
Optimisation of BT						
Yes	11,321 ± 2,829	<0.001	10,188 ± 2,100	0.001	10,695 ± 1,664	<0.001
No	12,964 ± 4,142		11,786 ± 2,912		12,871 ± 4,729	
Concomitant MTX at BT onset						
Yes	12,589 ± 3,690	0.516	10,201 ± 2,107	0.906	12,787 ± 5,182	0.322
No	12,346 ± 4,095		11,803 ± 2,925		11,800 ± 3,039	
Concomitant Leflunomide at BT onset						
Yes	12,962 ± 3,974	0.482	13,511 ± 0	0.263	11,829 ± 1,458	0.863
No	12,424 ± 3,882		11,521 ± 2,317		12,336 ± 4,422	
Concomitant GC at onset						
Yes	12,514 ± 3697	0.240	11,710 ± 1,501	0.343	13,081 ± 5,002	0.212
No	12,179 ± 4780		11,206 ± 2,964		11,472 ± 2,538	
Hospital admission						
Yes	14,639 ± 5,406	<0.001	12,594± 4,328	0.024	15,438 ± 7,724	0.004
No	11,644 ± 2,622		10,977 ± 2,243		11,592 ± 2,588	
Visits to Emergency Department						
Yes	12,546 ± 3,693	0.441	11,366± 3,381	0.808	12,789 ±4,845	0.292
No	12,503 ± 4,051		11201 ± 2,346		11,903 ± 3708	

AS: ankylosing spondylitis; BT: biological therapy; GC: glucocorticoid; MTX: methotrexate; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SD: standard deviation; n : number of patients; TNF: tumour necrosis factor.
[¥]Active smoker at the start of biological therapy.
[‖]Patients on treatment with a psychoactive drug at the start of biological therapy.

Results

Overall, 422 BT lines were analysed. Clinical, sociodemographic and pharmacological characteristics of patients are shown in Table I. The cohort of patients with RA was older, had a higher percentage of women, a higher percentage of pensioners, a higher number of comorbidities and higher illness activity (CRP and ESR) at the start of BT. In addition, a higher percentage of RA patients were on GC at the start of BT. The cohort of patients with PsA had a higher frequency of concomitant psychoactive drugs.

Table IV. Simple and multiple linear regression in patients with rheumatoid arthritis.

	Simple linear regression		Multiple linear regression	
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Sex (female)	-176.4 (-1,318.9 to 966.1)	0.761		
Comorbidities (Charlson Index)				
Between 0-3	713.9 (-489.6 to 1,917.4)	0.244	267.6 (-871.0 to 1,406.2)	0.643
Between 4-9 ≥10	2,619.6 (1,152.4 to 4,086.8)	0.001	398.4 (-1,249.7 to 2,046.4)	0.634
Smoking habit ¥	-1,130.9 (-2,697.5 to 435.8)	0.156		
Psychoactive drug intake ‖	-3,801.6 (-12,195.6 to 4,592.5)	0.372		
Employment status:				
Employed or homemaker/unemployed/ on sick leave or student	427.0 (-1,153.6 to 2,007.5)	0.595	-1,046.5 (-2,367.5 to 274.5)	0.120
Pensioner	1,299.5 (94.1 to 2,504.9)	0.035	331.7 (-880.9 to 1,544.4)	0.590
Time on the same BT (days)	-1.3 (-2.1 to -0.5)	0.002	-2.1 (-3.0 to -1.3)	**<0.001**
Type of BT				
Non anti-TNF-α group				
Anti-TNF-α group	-2,928.3 (-4,097.0 to -1,759.6)	<0.001	163.7 (-1,323.9 to -1,651.3)	0.828
Number of BT lines First BT line				
Second or successive BT lines	1,622.4 (590.8-2,654.1)	0.002	-124.5 (-1,171.7 to 922.6)	0.815
Administration of BT Day Hospital				
Outside of hospital	-4,187.3 (-5,474.1 to -2,900.4)	<0.001	-4,914.9 (-6,541.9 to – 3,288.0)	**<0.001**
Optimisation of TB	-1,643.4 (-2,804.9 to -482.0)	0.006	-168.8 (-1,342.0 to 1,004.5)	0.777
Concomitant MTX at onset	242.3 (-811.7 to 1,296.3)	0.651		
Concomitant Leflunomide at onset	537.6 (-1,225.6 to 2,300.9)	0.548		
Concomitant GC at onset	335.3 (-1,073.8 to 1,744.4)	0.639		
Hospital admission	3,041.6 (1,952.3 to 4,130.9)	<0.001	2,498.8 (1461.0 to 3,536.6)	**<0.001**
Visits to Emergency Department	43.0 (-1,018.2 to 1,105.2)	0.937		

B: standardised regression coefficient: BT: biological therapy; GC: glucocorticoid: MTX: methotrexate; TNF: tumour necrosis factor.
¥Active smoker at the start of biological therapy.
‖Patients on treatment with a psychoactive drug at the start of biological therapy.

The annual pharmacological cost of BT per patient was €10,250±2,343 for RA, €9,940±2,230 for AS and €10,500±2,395 for PsA (p= 0.355). The total cost (pharmacological plus non-pharmacological) per patient/year of BT was €12,494±3,865 for RA, €11,248±2,763 for AS and €12,263±35,155 for PsA (*p*=0.008).

One hundred and eighteen (54.9%) were first BT lines in RA, 71 (66.3%) in AS and 62 (62.0%) in PsA (*p*=0.120). In 58 (27%) RA patients, 36 (30.8%) AS patients and 27 (27.0%) PsA patients, the BT dosage had been optimised (low-dose outliers) (*p*=0.421). The mean (±SD) treatment duration with the same BT was 952.8 ± 657.0 days for RA patients, 1,055.4 721.7 days and 1,096.6±660.1 days for AS and PsA patients, respectively (*p*=0.154).

Table II shows the healthcare resources used by patients per disease per year of BT. RA patients visited the day hospital more frequently for the intravenous administration of BT and had a higher number of hospital admissions than AS and PsA patients. AS patients had fewer visits to the Rheumatology Department, a lower number of radiological tests were carried out on them and they showed a lower number of admissions than RA and PsA patients. The highest number of magnetic resonance imaging (MRI) scans per year of BT was performed on PsA patients.

The healthcare resource most commonly used by the patients was visits to the Outpatient Hospital Pharmacy (around 8 a year). No difference was observed among the three diseases.

Table III describes in detail the data about total costs for each disease. The concomitant use of psychoactive drugs resulted in an increased cost of BT only in the case of PsA patients. The number of comorbidities and the BT type according to their mechanism of action had an impact on the cost of patients with RA and PsA but not on those with AS. In the case of RA patients, first line BT implied a lower cost than successive lines, but no cost differences emerged for AS and PsA patients.

A direct relationship was found between BT persistence and cost in all the diseases studied. One additional day on the same BT reduced cost in €0.303 per day (*p*<0.001) in RA patients, in €0.374 per day (p<0.001) in AS patients and in €0.261 per day (*p*=0.009) in PsA patients.

Tables IV, V and VI show the results of the simple and multiple linear regression for each disease. To assess the influence of the BT, variable data

Table V. Simple and multiple linear regression in patients with ankylosing spondylitis.

	Simple linear regression		Multiple linear regression	
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Sex (female)	1,107.6 (-155.3 to 2,370.4)	0.085		
Comorbidities (Charlson Index)				
Between 0-3	1,372.0 (258.4 to 2,485.6)	0.016	783.7 (-160.2 to 1,727.5)	0.103
Between 4-9 ≥10	1,021.2 (-778.0 to 2,820.5)	0.263	631.7 (-911.5 to 2,174.8)	0.419
Smoking habit [¥]	-123.4 (-1,402.9 to 1,156.1)	0.848		
Psychoactive drug intake [‖]	692.1 (-4,867.0 to 6,251.1)	0.804		
Employment status:				
Employed or homemaker/unemployed/ on sick leave or student	538.9 (-823.4 to 1,904.3)	0.434		
Pensioner	731.9 (-1,015.8 to 2,479.6)	0.407		
Time on the same BT (days)	-1.4 (-2.1 to -0.7)	<0.001	-1.5 (-2.2 to -0.7)	**<0.001**
Number of BT lines				
First BT line				
Second or successive BT lines	-145.2 (-1,275.6 to 985.2)	0.799		
Administration of BT Day Hospital				
Outside of hospital	-1,2876.0 (-17,838.4 to -7,313.7)	<0.001	-10,580.7 (-15,175.4 to -5,986.0)	**<0.001**
Optimisation of TB	-1,602.6 (-2,690.0 to -515.1)	0.004	-285.7 (-1,436.2 to 864.9)	0.623
Concomitant MTX at onset	11.6 (-2,003.2 to 2,026.4)	0.991		
Concomitant Leflunomide at onset	1,990.6 (-2,676.1 to 6,657.4)	0.397		
Concomitant GC at onset	564.8 (-906.2 to 2,035.9)	0.448		
Hospital admission	1,616.9 (254.2 to 2,979.5)	0.020	1,636.0 (353.1 to 2,918.9)	**0.013**
Visits to Emergency Department	165.7 (-932.8 to 1,264.2)	0.765		

B: standardised regression coefficient: BT: biological therapy; GC: glucocorticoid: MTX: methotrexate; TNF: tumour necrosis factor.
[¥]Active smoker at the start of biological therapy.
[‖]Patients on treatment with a psychoactive drug at the start of biological therapy.

were grouped according to mechanism of action: anti-tumour necrosis factor (TNF)-α or non-anti-TNF-α therapies; dosage optimisation and place of administration of BT.

Discussion

To our knowledge, this is the first study that analyses in detail the direct costs generated by patients with RA, AS and PsA on BT. When total cost of each disease is considered, AS has a lower overall (pharmacological and non-pharmacological) cost than RA and PsA per BT year. However, when only the cost of BT is taken into account, there are no differences in cost, probably due to a lesser use of hospital resources by AS patients. In our study, the non-pharmacological cost represents between 12% and 18% of the direct costs of CIA.

Hospital admissions increased the total cost of CIA. The outpatient administration of BT and a longer BT persistence reduced costs for the Healthcare System. The use of non-anti-TNF-α drugs increases costs in PsA patients but not in those with RA or AS according to our results.

A study published in 2005 estimated that the average cost of RA was €3,845 per year of treatment (from €318 to €36,783) but only 17 out of the 301 studied patients were on BT. The direct costs breakdown in that study was similar to ours, in which admission costs represented 11% of the total and the cost of medical consultation 21% (35).

In another study on RA patients, also published in Spain, the direct costs were similar to ours (€6,663 in 6 months on etanercept, €7,569 in 6 months on adalimumab and €7,241 in 6 months on infliximab). The cost of BT represented between 80% and 85% of the total cost of the treatment and the main difference in costs for each BT resulted from the cost of the drug and the difference in the number of hospital admissions (10). The data gathered for our study are in contrast with those described in two studies carried out in the United States, which estimated annual direct costs of $26,883 and $24,978 for PsA and AS patients, respectively (18-19). These costs are significantly higher than those calculated in our study. However, the peculiarities of the American and the Spanish healthcare systems must be taken into account as well as the fact that the cost of drugs in the United States can be up to a 40% higher than in Spain.

In another study carried out in Germany, the annual cost of AS was estimated at €5,190 (12), although only 10% of patients were on BT. In the review of pharmacoeconomic studies conducted by D'Angiolella (15) *et al*., PsA costs varied significantly according to the country where the study took place and to whether the use of BT had been con-

Table VI. Simple and multiple linear regression in patients with psoriatic arthritis.

	Simple linear regression		Multiple linear regression	
	B (95% CI)	*p*-value	B (95% CI)	*p*-value
Sex (female)	889.3 (-79.6 to 2,572.1)	0.297		
Comorbidities (Charlson Index)				
Between 0-3	1,230.6 (-472.9 to 2,934.1)	0.155	1,330.3 (-276.2 to 2,936.8)	0.103
Between 4-9 ≥10	4,477.1 (1,503.2 to 7,451.0)	0.004	1,755.8 (-1,166.0 to 4,677.7)	0.236
Smoking habit [¥]	-619.6 (-2,629.6 to 1,390.4)	0.539		
Psychoactive drug intake [‖]				
Employment status:				
Employed or homemaker/unemployed/ on sick leave or student	-773.1 (-3,293.6 to 1,747.4)	0.543		
Pensioner	375.5 (-2,291.4 to 3,042.3)	0.780		
Comorbidities (Charlson Index)				
Between 0-3	1,230.6 (-472.9 to 2,934.1)	0.155	1,330.3 (-276.2 to 2,936.8)	0.103
Between 4-9 ≥10	4,477.1 (1,503.2 to 7,451.0)	0.004	1,755.8 (-1,166.0 to 4,677.7)	0.236
Time on the same BT (days)	-1.5 (-2.8 to -0.3)	0.017	-1.7 -3.0 to -0.45)	**0.009**
Type of BT1				
Non TNF-α group				
Anti-TNF-α group	-4,180.3 (-7,963.9 to -396.7)	0.031	-3,128.7 (-6,885.4 to 628.1)	0.101
Number of BT lines				
First BT line				
Second or successive BT lines	456.2 (-1,281.4 to 2,193.9)	0.604		
Administration of BT Day Hospital				
Outside of hospital	-3,392.6 (-6,632.3 to -153.0)	0.040	-2,322.3 (-5,576.3 to 931.6)	0.160
Optimisation of TB	-2,176.0 (-4,027.7 to -324.2)	0.022	-698.6 (-2,583.5 to 1,186.3)	0.463
Concomitant MTX at onset	987.3 (-690.6 to 2,665.2)	0.246		
Concomitant Leflunomide at onset	-506.4 (-3,851.6 to 2,838.9)	0.764		
Concomitant GC at onset	1,608.8 (-101.6 to 3,319.2)	0.065	1,254.3 (-267.4 to 2,776.1)	0.105
Hospital admission	3,846.5 (1,787.7 to 5,905.2)	<0.001	3,787.7 (1,763.5 to 5,811.9)	**<0.001**
Visits to Emergency Department	886.3 (-810.4 to 2,583.0)	0.302		

B: standardised regression coefficient: BT: biological therapy; GC: glucocorticoid: MTX: methotrexate; TNF: tumour necrosis factor.
[¥] Active smoker at the start of biological therapy.
[‖] Patients on treatment with a psychoactive drug at the start of biological therapy.

sidered. This last factor has the greatest influence on the cost of the disease.

Another published study on the factors likely to influence the cost of RA identified the severity of the disease, patients' lifestyle, age and socioeconomic status as predicting factors for a higher cost (8). However, another study did not find a relationship between the severity of this disease and higher healthcare costs (5). Other authors have observed that patients with RA in remission are less costly for the Healthcare System in terms of hospital admissions, visits to Emergency Department and mortality but when only direct costs are taken into account and a BT treatment is deemed necessary to attain remission, the current cost of the drugs is so high that it renders the economic benefits of remission not financially worthy (11).

In another Spanish study, the use of BT, comorbidities and patients' age were identified as predictive factors for a higher RA cost. When the BT patients´ subgroup was analysed, these predictive factors were age, female sex, disease activity and disease duration (9). In our study, disease activity could not be assessed using objective measurement methods such as Disease Activity Score (DAS) due to incomplete activity data in the clinical records. Regarding the influence of age and sex on the cost of the disease, we did not find any relationship. The use of BT in an optimised dosage resulted in lower costs of all CIA, which shows that a lower dose than that recommended in the specification sheet did not imply an increase in the use of other healthcare resources. According to a study published in 2017, the use of BT in optimised dosage is cost-effective. In our case, the decrease in BT dosage implied a lower total cost but when cost-influencing factors were considered, the optimised dosage was not a determining factor in cost reduction (36).

Our data on a decrease in costs as the BT increases in duration are similar to those published by Dalén (37) *et al*. and Sruamsiri (38) *et al*., who observed that persistence to BT was a positive factor in terms of hospital resource use such as outpatient consultations, admissions

and the use of drugs not pertaining to the synthetic DMARDs group.

An increase in comorbidities only influenced treatment costs in the case of PsA, in contrast to what is observed in a study published in the United States (13), in which age and a higher number of comorbidities, both in AS and PsA patients, were predictive factors for increased costs.

One of the limitations of our study was the fact that it did not include an estimation of the indirect costs of the disease. However, a systematic review of direct and indirect costs of psoriasis and PsA estimated a yearly total cost of between $10,924 and $17,050 respectively, where direct costs were the most significant (14). A Spanish study analysing the costs of RA patients reached similar results, a 74% of which corresponding to direct costs and a 26% to indirect costs (37).

Our study also has other limitations such as the fact that it was carried out as a unicentric study, our time horizon was limited to 8 years and the economic data on hospital resource use were from 2012 while drug costs corresponded to 2016. Despite the current interest of the use of biosimilars and their positive economic impact, at the time of data collection for our study there were no patients on biosimilar treatment in our hospital. We believe nevertheless that in spite of these weaknesses, our study brings a new light on the real significance of BT costs in relation to other costs related to the use of hospital resources and paves the way for the development of a new strategy to diminish the cost of these diseases. Future studies should analyse the influence of biosimilars in the cost of these diseases.

Conclusion

Our research results indicate that, in patients on BT, the cost of AS for the Healthcare System is lower than that of RA and PsA when only the direct costs of the disease are taken into account. The cost of the BT is the factor with the highest impact on the overall cost of these diseases. Preventing a hospital admission, the subcutaneous administration of the drug and a higher persistence to the BT are all factors contributing to lower costs for the Healthcare System. Comorbidities, patients' age and disease duration do not seem to have an impact on the direct costs of the disease.

Future studies should analyse the influence of the indirect costs of these diseases such as loss of productivity and the introduction of biosimilars in CIA treatments.

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