Counting Costs under Severe Financial Constraints: A Cost-of-Illness Analysis of Spondyloarthropathies in a Tertiary Hospital in Greece

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ABSTRACT. ***Objective.*** To investigate the total annual direct cost of patients with spondyloarthritis (SpA) in Greece.

Methods. Retrospective study with 156 patients diagnosed and followed up in the rheumatology clinic of the University Hospital of Ioannina. Sixty-four had ankylosing spondylitis (AS) and 92 had psoriatic arthritis (PsA). Health resource use for each patient was elicited through a retrospective chart review that documented the use of monitoring visits, medications, laboratory/diagnostic tests, and inpatient stays for the previous year from the date that the review took place. Costs were calculated from a third-party payer perspective and are reported in 2014 euros.

Results. The mean ± SD annual direct cost for the patients with SpA reached €8680 ± 6627. For the patients with PsA and AS, the cost was estimated to be €8097 ± 6802 and €9531 ± 6322, respectively. The major cost was medication, which represented 88.9%, 88.2%, and 89.3% of the mean total direct cost for SpA, AS, and PsA, respectively. The annual amount of the scheduled tests for all patients corresponded to 7.5%, and for those performed on an emergency basis, 1.1%. Further, the cost for scheduled and emergency hospitalization, as well as the cost of scheduled visits to an outpatient clinic, corresponded to 2.5% of the mean total annual direct cost for the patients with SpA.

Conclusion. SpA carries substantial financial cost, especially in the era of new treatment options. Adequate access and treatment for patients with SpA remains a necessity, even in times of fiscal constraint. Thus, the recommendations of the international scientific organizations should be considered when administering high-cost drugs such as biological treatments. (J Rheumatol First Release April 1 2015; doi:10.3899/jrheum.141277)

Key Indexing Terms:
SPONDYLOARTHROPATHIES PSORIATIC ARTHRITIS ANKYLOSING SPONDYLITIS
ANNUAL COST DIRECT COST

The term *spondyloarthritis* (SpA) refers to a heterogeneous group of rheumatic diseases with common clinical and laboratory features. Its main clinical manifestation is inflammatory lumbar pain. The diseases can also manifest with symptoms other than axial involvement, such as asymmetrical oligoarthritis, polyarthritis indistinguishable from rheumatoid arthritis (RA), enthesitis, dactylitis, as well as with extraarticular manifestations with symptoms from involvement of the eye, respiratory system, cardiovascular system, gastrointestinal system, and others[1,2,3]. The family of SpA includes ankylosis spondylitis (AS), psoriatic arthritis (PsA), inflammatory arthritis-associated inflammatory bowel disease, juvenile SpA, reactive arthritis, and undifferentiated SpA[4].

The etiology of SpA is largely unknown, and reflects a complexity of environmental, immunological, and genetic interactions. There is a strong association between the susceptibility of SpA and tissue antigen HLA-B27[5,6,7]. Several gastrointestinal and genitourinary pathogen species such as *Campylobacter*, *Chlamydia*, *Salmonella*, and *Shigella* have been associated[8,9].

The prevalence of SpA in Europe has been reported as 0.3–1.9%[4,9,10,11,12]. The prevalence and incidence, according to different studies, vary because of differences in the genetics (HLA-B27) of the population, environmental

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Accepted for publication February 24, 2015.

triggers, and differences in study designs. In addition, there are no widely well-accepted classification criteria. The Assessment of SpondyloArthritis International Society (ASAS) has published[13,14] criteria for the classification of both axial and peripheral SpA.

SpA is a family of chronic diseases that require serious monitoring and managing because they can lead to limitations of functional capacity, decreased ability to work, and reduced overall quality of life, with significant social and financial cost. At the same time, the introduction of anti-tumor necrosis factor (TNF) biologic agents in the treatment of SpA contributes to the increase in the financial burden of these diseases[15,16,17].

In the United States, it is estimated that for 1.4 million patients with PsA or psoriasis, the total annual cost has risen to US $649.6 million. The cost of outpatient visits accounted for US $86.6 million, and US $357.2 million and US $30.5 million for over-the-counter medications and hospitalization, respectively[18,19]. According to the literature, the disease is also reported to entail a significant financial burden in European countries, as well as in Canada, Brazil, Mexico, and others[20].

In light of this and in the absence of a previous estimate for Greece, a country under severe financial constraints, the purpose of our study was to estimate the total annual direct cost of SpA within the context of the Greek healthcare setting.

MATERIALS AND METHODS

The sample included patients who had visited the outpatient rheumatology clinic of the tertiary University Hospital of Ioannina on a scheduled or an emergency visit between June 1, 2013, and December 31, 2013. From 166 diagnosed patients according to the ASAS criteria for SpA, 156 were recruited for the study. Six patients had enteropathic arthritis and were evaluated by a gastroenterologist. These patients were excluded because of a lack of data. Four patients with undifferentiated SpA were also excluded. Three of them refused any diagnostic and therapeutic intervention, and 1 was lost to followup. Sixty-four patients were diagnosed with AS and 92 patients with PsA. The patients with PsA fulfilled the CASPAR (Classification for Psoriatic Arthritis) criteria, and those with AS, the New York classification criteria[21,22]. For these patients, we investigated retrospectively their medical records for 1 year, and we recorded the information on health resource use (reported in detail below).

For each patient, the health resource use/consumption pattern was elicited through a retrospective chart review for a period of 365 days before the date of the review. Data also included the number of monitoring visits (scheduled or unscheduled) and days of inpatient hospitalization, and laboratory, imaging, and other tests that were conducted on a scheduled or emergency basis. In particular, total annual direct laboratory use included the tuberculosis skin test (Mantoux test), blood examinations, radiographs, computed tomography, magnetic resonance imaging, dual-energy X-ray absorptiometry, ultrasound, gastroscopy, colonoscopy, and electromyography. Resource use and subsequent costs were disaggregated for the tests conducted on scheduled patients and those conducted on an emergency basis.

For the patients treated with biologic agents administered in the hospital, the cost of the nursing staff and the cost of consumable materials used for the infusion were also recorded. It should be mentioned that only the costs that were attributable to SpA were recorded and not those related to the comorbid conditions.

All resources, including medications, were costed under the perspective of the third-party payer by applying all relevant prices and tariffs, as reported by the latest applicable official price lists at the time that the analysis took place. Cost values are reflected in euros as of 2014.

The study was approved by the institutional ethics committee and all patients provided informed consent.

RESULTS

The mean ± SD age of the patients was 52 ± 13 years and the mean ± SD disease duration was 17 ± 11 years. All demographic data of the patients are shown in Table 1.

From the 64 patients with AS, 48 of them were under treatment with biologic disease-modifying antirheumatic drugs (DMARD). Of the 92 patients with PsA, 50 patients were treated with biologic DMARD and 42 were treated with nonbiologic DMARD (Table 1).

From the conducted study, the mean annual direct cost per patient with SpA reached €8680 ± 6627. For the subgroup of patients with PsA and AS, the annual direct cost was estimated to be €8097 ± 6802 and €9531 ± 6322, respectively. A major part of the cost was the medications; in our study, 88.9%, 88.2%, and 89.3% of the mean total direct cost represented pharmaceutical expenditures for patients with SpA, AS, and PsA, respectively. We found that the total annual pharmaceutical expenditures for each patient reached €7717 ± 6615. Of this total cost, 97.1% (€7499 ± 6607) was the cost of the treatment with biologic DMARD, and only 2.8% (€218 ± 455) was the cost of the annual nonbiologic pharmaceutical expenditures for the whole group of patients with SpA. Analysis of the subgroups showed that for the 92 patients with PsA, the total cost of pharmaceuticals was €7234 ± 6890, of which 95.1% represented the cost of treatment with biologic DMARD (€6880 ± 6847). The cost of nonbiologic pharmaceutical treatment was 4.9% (€353 ±

Table 1. Characteristics of the patients with SpA. Values are n (%) unless otherwise specified.

Characteristics	Total	PsA	AS
Demographic features			
Total no. patients included	156	92	64
Male/female	107/49 (68/32)	50/42 (54/46)	57/7 (89/11)
Age, yrs, mean ± SD	52 ± 13	55 ± 14	51 ± 12
Disease duration, yrs, mean ± SD	17 ± 11	15 ± 11	19 ± 12
Diagnosis			
PsA	92 (59)	92 (100)	—
AS	64 (41)	—	64 (100)
Treatment			
Patients receiving biologic DMARD	98 (63)	50 (54)	48 (75)
Patients not receiving biologic DMARD	58 (37)	48 (52)	16 (25)
Methotrexate	60 (38)	54 (58)	6 (9)
Cyclosporine	18 (11)	18 (19)	0 (0)
Leflunomide	9 (5)	9 (9)	0 (0)

SpA: spondyloarthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; DMARD: disease-modifying antirheumatic drugs.

551). The patients with AS showed a slightly higher pharmaceutical expenditure: €8413 ± 6186, of which 99.7% represented the cost of biologic DMARD (€8388 ± 6191) and 0.3% the expenditure for nonbiologic treatment (€24 ± 84).

In the present study, the total annual direct cost included the cost of laboratory tests, imaging, and other procedures (Table 2 and Table 3), as well as the cost of hospital care and clinical examination in the outpatient clinic (Table 4). The mean annual cost of the scheduled tests for each of the 156 patients corresponded to 7.5% (€655 ± 518) of the mean annual direct cost. The cost for the tests performed on an emergency basis represented 1.1% (€98 ± 265) of the latter.

The data showed small differences for the subgroup of patients with AS. The annual cost of scheduled tests for the current subgroup corresponded to 7.5% (€720 ± 503) of the total. The tests performed on an emergency basis represented 0.65% of the mean annual direct cost (€62 ± 144). For patients with PsA, the scheduled tests also represented 7.5% of the mean annual direct cost. For the tests conducted on emergency basis for these patients, the cost was slightly higher, reaching 1.5% (€123 ± 323) of the total mean annual direct cost.

Further, the cost of scheduled and emergency hospitalization, as well as the cost of scheduled visits to the outpatient clinic, corresponded to 2.5% of the mean total annual direct cost for the patients with SpA. For the patients with PsA, it represented 1.7%. For the patients with AS, the rate was up to 3.65% of the mean total annual direct cost.

Finally, the annual cost of biologic agents in Greece was estimated, for the 62 patients receiving infliximab, to be €11,286 ± 4016. The cost was higher in patients with PsA compared with those with AS (€12,190 ± 3886 and €10,633 ± 4036, respectively). For the biologic agents that were administered subcutaneously [etanercept (ETN) and adalimumab (ADA)], the mean price was higher. For each of the 36 patients receiving ETN or ADA, the cost reached €12,643 ± 1522. For the patients with PsA, the total annual amount was €12,886 ± 920, and for the 12 patients with AS, it reached €12,757 ± 973.

DISCUSSION

SpA incurs a high economic burden, similar to other rheumatologic diseases[23]. To our knowledge, the present study is the first to analyze the direct cost of SpA, and more particularly PsA and AS in Greece, and one of the very few to include patients receiving biologic agents, despite the limits of a retrospective study. Considering the financial environment and the spending cuts in the public health sector as a result of the financial crisis, understanding the financial burden associated with these diseases is crucial for optimal use of scarce healthcare resources.

As previously stated, the total annual direct cost per patient of these diseases reached €8680 ± 6627. For the patients with PsA, this cost was estimated to be €8097 ± 6802, and €9531 ± 6322 for those with AS. It should be noted that our clinic is a reference center and most of the patients with PsA were refractory to treatment with synthetic DMARD. The latter may result in an overestimation of the cost. More than 88% of the total annual cost of the 2 diseases represents the cost of pharmaceutical treatment and includes the cost of biologic agents. The total annual cost per patient of the biologic agents was €10,633 ± 4036 to €12,886 ± 920, depending on the agent that was administered.

Table 2. Annual costs (€) by specific tests on a scheduled and emergency basis in patients with SpA. Values are mean ± SD.

Tests	Cost of Scheduled Tests			Cost of Emergency Tests		
	Total	PsA	AS	Total	PsA	AS
Blood examinations	421 ± 333	441 ± 410	394 ± 168	86 ± 252	108 ± 308	54 ±132
Radiographs	9.1 ± 23.9	6.8 ± 9.5	12 ± 35	0.29 ± 1.4	0.4 ± 1.7	0.12 ± 0.71
DEXA	18.2 ± 37	21.2 ± 39.9	14 ± 32	0.33 ± 4.2	0.5 ± 5.5	0
CT	22.3 ± 49.6	20.8 ± 44.1	24 ± 56	1.8 ± 13.8	3 ± 17.9	0
MRI	124 ± 254	69 ± 166.7	203 ± 329	9.1 ± 53	10.3 ± 59.9	7.4 ± 41
Ultrasound	43 ± 76	41.2 ± 65.5	45 ± 90	0	0	0
Gastroscopy/colonoscopy	16 ± 52	9.2 ± 31.8	26 ± 72	0	0	0

SpA: spondyloarthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; DEXA: dual-energy X-ray absorptiometry; CT: computed tomography; MRI: magnetic resonance imaging.

Table 3. Annual total costs (€) of tests done on a scheduled and emergency basis in patients with SpA. Values are mean ± SD.

Annual Costs	Total	PsA	AS
Annual cost of scheduled tests	655 ± 518	610 ± 526	720 ± 503
Annual cost of emergency tests	98 ± 265	123 ± 323	62 ± 144

SpA: spondyloarthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis.

Table 4. Annual financial burden (€) for the national healthcare system (hospitalization and outpatient clinic). Values are mean ± SD.

Type of Care	Total	PsA	AS
Scheduled visits to outpatient clinic	24 ± 19	22 ± 23	26 ± 11
Scheduled hospital care	194 ± 352	153 ± 423	253 ± 199
Emergency hospital care	20 ± 82	21 ± 87	17 ± 76

PsA: psoriatic arthritis; AS: ankylosing spondylitis.

Comparing results from various studies is challenging because of the differences in methodology and in healthcare systems in different countries. According to Huscher, *et al*, the mean ± SD direct annual cost for patients diagnosed with PsA reached €3156 ± 4118, not including patients treated with biologic agents[24]. In the study by Zhu, *et al*[25], the annual direct cost of patients with PsA, also naive to biologic agents, reached US $4141 for every patient. It should be mentioned that the design of Zhu, *et al*'s study and the variables that were included in the direct cost were quite similar to the variables included in our study. According to Zhu, *et al*'s study, the cost of diagnostic tests represented 10% of the total annual direct cost, a rate similar to the 7.5% in our study. However, Zhu, *et al* reported a rather low cost contribution of medications to the total cost per patient (10%), a finding that can be attributed to the exclusion of patients undergoing newer (biologic) treatments[25]. In a study by Poole, *et al* in 2010, the mean annual direct cost for patients with PsA not treated with biologic agents ranged from £1446 ± 1756 to £4832 for the most severely affected[26].

All these studies showed lower values for the annual direct cost than those estimated by our present study. An important factor is that these studies included patients naive to biologic agents. We found that the cost of biologic agents reaches about €6880 ± 6847 and represents more than 95% of the total annual cost of pharmaceutical expenditures in patients with PsA. In the study by Olivieri, *et al*, the use of TNF inhibitors led to a significant increase in the direct cost by €5052 because of an increase in drug costs[27]. Finally, in a study by Kvamme, *et al*, it is estimated that the direct cost of patients with PsA treated with biologic agents for 2 years reached €37,159 in comparison with €6300 for those treated with synthetic DMARD for the same 2-year period. The direct cost for these patients exceeded the annual cost that our study estimates[28]. It should be noted, however, that our present study, as well as the ones reported here, focused solely on the costs of treatment, and did not provide estimates with regards to treatment efficacy — the other major part of every treatment approach.

For the other part of the study sample, i.e., patients with AS, the comparison of the different studies is also challenging because of the reasons mentioned (differences in the design and methodology used, and the different indications valid in the various countries for the administration of biologic agents). However, some rough comparisons can be made. Specifically, in the study by Torres, *et al*[29], the total mean annual direct cost (medical and nonmedical) was estimated to be US $2065, again a value lower than the one we found. The Torres, *et al* study included only patients not receiving biologic DMARD. The cost of medication represented 91.7% of the estimated total direct cost, similar to the results of our study[29].

In the same way, a study that estimates the financial burden of AS in the Czech Republic by Petříková, *et al*[30] estimated average total direct cost as €2588. The main reason for this difference is that in the Czech Republic, the administration of biologic DMARD is significantly less compared to the average proportion of patients with AS treated with biologic DMARD in the European Union and the United States. In that study, the proportion of the patients receiving biologic DMARD was 6.3%, a rate significantly lower than the 75% in our study. Also, it must be highlighted that according to the study by Petříková, *et al*, the average cost of treatment with a biologic agent per year per patient was estimated to be €17,046, a figure that exceeds the cost from our study[30].

In the study by Boonen, *et al*[31], which estimated the direct cost of AS in the Netherlands, France, and Belgium, the estimated mean annual direct cost was €2837, €2570, and €1790, respectively. In the latter, patients receiving biologic DMARD were not included[31]. In the study by Ackland, *et al*, which estimated the cost of care in patients with AS and RA in Turkey, the mean annual direct cost was €3561. The cost in the Ackland, *et al* study is smaller than that estimated in our study, probably because of the relatively small proportion of the patients receiving biologic DMARD: 8%, 8.62%, and 8.33% for those receiving infliximab, ETN, and ADA, respectively[32].

A limitation of this analysis is that the sample of patients and thus the estimate of costs per patient were derived from a specialized point of care. A discrepancy could exist between the estimates presented in our study and the cost in other points of care in the system. Although this discrepancy is very difficult to quantify, its potential existence should be taken into account when interpreting and generalizing the results for the entire population of patients in Greece.

It should be noted that SpA represent a significant financial burden, especially for a country under severe financial constraints. To endure the mandates for cost reduction and general austerity that are currently (and for the visible future) implemented in Greece, novel approaches are necessary with a purpose of securing adequate access to health services and proper treatment for SpA. The latter certainly constitutes an area of further research. Finally, the recommendations of the international scientific organizations should be considered when administering high-cost drugs such as biological treatments.

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