Clinical profile and direct medical cost of care of adults presenting with systemic lupus erythematosus in Italy

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Abstract

Objective

To determine the clinical profile and estimate the annual direct medical cost of care of adult patients with active, autoantibody positive systemic lupus erythematosus (SLE) in Italy.

Methods

A two-year, retrospective, multicentre, observational study was conducted from January to May 2011. Patients' characteristics, SLE disease activity and severity, rate of flares, healthcare consumption (e.g. medications, etc.) were evaluated. Medical costs were assessed from the Italian National Health Insurance perspective.

Results

Four centres enrolled 96 eligible patients, including 85.4% women. Patients were equally stratified per disease severity (severe SLE: 51%). The mean (SD) age was 42.9 (13.8) years.

At baseline, SLE duration was 12.6 (7.2) years. The mean (SD) SELENA-SLEDAI score was higher in severe than in non-severe patients 9.2 (6.4) vs. 3.3 (3.1) ($p<0.001$). The mean (SD) SLICC/ACR index score was similar in the two subgroups: 0.4 (0.8) vs. 0.3 (0.8). Over the study period, severe patients experienced on average 0.73 (0.56) flares/year and non-severe patients 0.57 (0.63). The annual medical cost was 1.6 times higher in severe than in non-severe patients (€2,101 vs. €1,320; $p=0.031$). The cost of medications was also 2.5 times higher in severe patients (€1101 vs. €445, $p=0.007$). Low C3/C4 complement levels and each severe flare incremented the annual cost of €550 ($p=0.011$) and €465 ($p=0.02$), respectively.

Conclusion

The medical cost of SLE in Italy is related to disease severity and flares. Medications identified as the main cost drivers, and low C3/C4 complement levels and severe flares as the main cost predictors, increased significantly the cost of SLE management.

Key words

systemic lupus erythematosus, SLE, clinical manifestations, flares, health resources, costs, immunosuppressants, biologics, hospitalisation.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by alternating periods of activity (relapses) and remission. Various organs may be involved with activity or damaged (skin, joints, lungs, kidneys, heart and brain), and the disease may present with a large range of symptoms and clinical manifestations (1, 2). The average prevalence of SLE estimated in four European countries, including Italy, was near 43 per 100 000 people (3-6).

European and international recommendations suggest the use of different therapeutic classes of drugs, alone or in combination according to the patient's clinical profile, and may include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalar-ials, and immunosuppressants (7, 8). Biologics, mainly rituximab, have been used in the last years in Europe, particularly for treating refractory disease (9, 10). One biologic drug, belimumab, was approved for SLE (11); others are in development or are used as off-label treatment (9).

Data on SLE care management, especially clinical profiles and their associated medical costs, do not exist for Italy and are limited for the other European countries (12-14). A recent study mentioned the few studies evaluating costs by disease severity, disease manifestations or associated with specific treatments (15). Further research identifying the reasons of variation of costs will contribute to improved use of new therapies and development of clinical management strategies.

The objectives of this study were to describe the clinical characteristics of SLE adult patients presenting with severe and non-severe active, autoantibody positive disease, and to evaluate the annual medical cost of SLE care management associated to these disease profiles in Italy. Cost drivers and cost predictors were also analysed.

Patients and methods

The study comprised two phases conducted in parallel: the main and ancillary studies.

Main study design

The LUpus erythematosus Cost of Illness in Europe study (LUCIE, GSK study GHO-09-2521, etrack number BEL114431) is a two-year, multi-centre, retrospective chart review of data collected in patients' medical files. It was conducted in five countries: France, Germany, Italy, Spain and the United Kingdom.

In Italy the study was conducted in reference care rheumatology settings specialising in SLE management, from January to May 2011. Five centres were expected to participate and include an average of 20 SLE patients each with active, autoantibody positive disease (ANA, anti-ENA and anti-dsDNA), to establish a 100-patient sample. Three centres included seven to twenty-two patients and a fourth included fifty patients to compensate for the withdrawal of a fifth centre.

Medical records were screened from January to June 2008 to identify a visit where patients met the inclusion criteria, and taken as inclusion/baseline visit (16). Patients' disease activity and severity were assessed at baseline. SLE disease was considered active in patients meeting one of the two following criteria: 1) one change in treatment related to SLE activity (increase in dose and/or new treatment) and/or occurrence of new manifestation or worsening of clinical symptoms of SLE, or 2) presence of one positive biomarker of SLE activity (anti-dsDNA antibodies and/or C3 or C4 below normal) and one clinical and/or haematological feature of SLE.

Eligible patients were then stratified by disease severity. Each centre enrolled an equal number of severe or non-severe patients. SLE disease was considered severe in patients with at least one major organ domain involved at inclusion (renal, neurological, cardiovascular or respiratory), and requiring prednisone equivalent dosages >7.5 mg/day and/or immunosuppressants.

Patient data were collected over a two-year period (± 3 months).

The study followed local legal requirements: it was approved by the four Ethics Committees corresponding to the participating hospitals, and all patients signed the written informed consent before inclusion.

Ancillary study design

The ancillary study aimed to evaluate in 'real life' the proportion of SLE patients presenting with severe and non-severe disease among patients with active, autoantibody positive disease of the overall SLE national population. It was conducted in three participating centres. Real life proportions were used to adjust the cost of care management and ensure that it was representative for the active SLE national population.

Disease activity and organ damage assessment

Disease activity and organ damage were retrospectively evaluated at baseline using the SELENA-SLEDAI instrument (17) and the SLICC/ACR damage index (18), respectively.

Definition, identification and severity of a flare

The occurrence and severity of flares was assessed by treatment changes (*i.e.* increasing dose of corticosteroids and/or initiating a new SLE treatment) and/or hospitalisation, using the SELENA-SLEDAI Flare Index (SFI) (19) at baseline, and an adapted version during the follow-up period.

Since it was not possible to identify precisely the end of a flare, in the case of two consecutive flares the second flare was considered as a new flare if it occurred more than 60 days after the beginning of the first flare.

Healthcare resource use evaluation and cost calculation

Direct annual medical costs were assessed using Italian National Health Insurance prices extracted from the official unit costs national databases available in 2011 (Table I).

Healthcare resource utilisation (*e.g.* medications, laboratory tests, hospitalisations) was collected for each patient from their medical file over the two-year study period. Unit costs were attributed per category to each unit of medical resource consumed to convert them into monetary values. Costs were pooled per resource category and divided by the corresponding number of patients. The total medical cost of SLE management was calculated for each patient considering his/her specific individual number of months of follow-up, and expressed as a mean annual value.

Table I. Names of the Italian official databases of unit costs and types of healthcare resources.

Name of the Italian official database	Type of healthcare resources	Official source/address
National visits formulary and Age. Na.S: outpatient specialist services	Laboratory test, biopsies, imaging tests, visits, drugs	Ministero della Salute Tariffe regionali 2008 (median between Regions)
Ricoveri ospedalieri (SDO)	Hospital stays	DRG- Ministero della Salute; Tariffa unica convenzionale per le prestazioni di assistenza ospedaliera (Versione 24° anno 2009)
AIFA: Agenzia Italiana del farmaco	Drugs	http://farmaco.agenziafarmaco.it/index.php

Statistical analysis

Statistical analysis was performed using the SAS system version 9.1 (SAS Institute Inc., Cary, NC, USA) in Windows™ operating system support. Data were analysed on the overall sample and then stratified by disease severity for severe and non-severe subgroups. The two sample *t*-test or Mann-Whitney test were used for quantitative variables and the chi-square test or Fisher's exact test for qualitative variables. Statistical significance was set at 0.05.

Multivariate regression models were developed to identify the predictors of the annual direct total direct medical cost, and to estimate the additional cost associated to them. The annual total cost of SLE (dependent variable) was normalised using a logarithmic transformation. Univariate regression models were performed for each independent variable and a *p*-value threshold of 0.1 was applied for selecting variables to be included in the multivariate model and assessing the possible colinearity between selected independent variables. The backward selection method was used to determine the best fitting model to predict annual direct medical costs.

Results

A total of 96 eligible patients were enrolled, 49 severe (51%) and 47 non-severe (49%). The mean (SD) follow-up study duration was 25.2 (3.2) months and was not significantly different between severe and non-severe patients.

Baseline characteristics

Table II shows the demographics and patients' clinical profile.

The study population comprised 82 females (85.4%) and 14 males (14.6%). Males were 3.5 times more frequently present among severe patients (p=0.026). The mean (SD) age was 42.9 (11.7) years. Severe patients were on average five years younger than those non-severe (40.3 *vs.* 45.6 years, p=0.026). The mean weight was 68.1 (7.0) kg. The mean disease duration, 12.6 (7.2) years, was not significantly different between the two subgroups.

The mean (SD) SELENA-SLEDAI score, 6.3 (5.9), was higher in severe than in non-severe patients (p<0.001). In addition, the proportion of patients with a SELENA-SLEDAI score ≥10 or with ≥3 systems involved was also higher in severe patients (p<0.001 and 0.026, respectively). As per study design, the proportions of active major organs involved, especially renal and CNS, were significantly higher in severe patients.

The mean (SD) SLICC/ACR damage index score, 0.4 (0.3), was similar in the two subgroups. In fact, only 24.5% of severe and 14.9% of non-severe patients had SLICC/ACR damage index score >0. The most frequently damaged system was the musculoskeletal system (11.5%), followed by the pulmonary and neuropsychiatric systems (5.2% each). Damaged neuropsychiatric domain was only observed in severe patients.

Autoantibodies tests were conducted for almost all patients (94.8%). ANA were positive in all patients tested. Anti-dsDNA, anti-ENA (including anti-Sm, anti-RNP, anti-La, anti-Ro) and antiphospholipid antibodies were positive in 63.9%, 63.1% and 51.6% of

Table II. Baseline characteristics: demographics and patients' clinical profile.

		Severe patients (n=49)		Non-severe patients (n=47)		*p*-value
Demographics						
Age (years)	Mean (SD)	40.3 (9.3)		45.6 (13.4)		0.026
	Median	39.0		41.5		
	Min - Max	23 - 64		23 - 74		
Gender	Females	38	77.6%	44	93.6%	0.026
	Males	11	22.4%	3	6.4%	
Disease duration (years)	Mean (SD)	11.3 (7.3)		13.9 (6.9)		0.083
SELENA-SLEDAI						
Score (continuous)	Mean (SD)	9.2 (6.4)		3.3 (3.1)		<0.001
Score (categorical)	≥ 10	21	42.9%	3	6.4%	<0.001
Systems involved	≥ 3 systems	11	22.4%	3	6.4%	<0.026
Systems with activity(*)	Immunology	40	81.6%	27	57.4%	0.010
	Renal	30	61.2%	9	19.1%	<0.001
	Mucocutaneous	5	10.2%	7	14.9%	0.487
	CNS	6	12.2%	0	0.0%	0.027
	Musculoskeletal	4	8.2%	2	4.3%	0.678
	Haematological	2	4.1%	4	8.5%	0.431
	Constitutional	2	4.1%	1	2.1%	1.000
	Cardiovascular & respiratory	3	6.1%	0	0.0%	0.242
	Vascular	2	4.1%	1	2.1%	1.000
SLICC/ACR Index						
Score (continuous)	Mean (SD)	0.4 (0.8)		0.3 (0.8)		0.436
Score (categorical)	0	37	75.5%	40	85.1%	0.535
	≥ 1 system	12	24.5%	7	14.9%	
Systems damaged*	Musculoskeletal system	4	8.2%	7	14.9%	0.301
	Neuropsychiatric system	5	10.2%	0	0.0%	0.056
	Pulmonary system	4	8.2%	1	2.1%	0.362
	Ocular system	2	4.1%	2	4.3%	1.000
	Cardiovascular system	1	2.0%	1	2.1%	1.000
	Peripheral vascular system	2	4.1%	1	2.1%	1.000
	Renal system	0	0.0%	0	0.0%	-
	Skin system	0	0.0%	0	0.0%	-
	Gastrointestinal system	0	0.0%	0	0.0%	-
	Diabetes	0	0.0%	0	0.0%	-
	Premature gonadal failure	0	0.0%	0	0.0%	-
	Malignancy	0	0.0%	0	0.0%	-
Medications						
	Antimalarials	18	36.7%	34	72.3%	<0.001
	Corticosteroids	45	91.8%	39	83.0%	0.190
	Immunosuppressants	43	87.8%	18	38.3%	<0.001
	Biological drugs	0	0.0%	1	2.1%	0.490
	NAIDS	7	14.3%	7	14.9%	0.933
	Anti-osteoporotic drugs	9	18.4%	16	34.0%	0.080

This table presents the demographics (age and gender) and patients' clinical profile (disease duration, SELENA-SLEDAI and SLICC/ACR scores and number of systems involved and damaged) expressed by disease severity.
The percentages were calculated based on the number of patients with valid data.

patients, respectively. The proportions of antibodies positive patients were not different between the two subgroups. Finally, C3 and C4 serum complement levels were below normal range in 56.0% and 45.8% of patients, respectively. The levels of C3 were more frequently below normal in severe patients (71.4% *vs*. 40.5%, p=0.004).

At baseline, corticosteroids, immunosuppressants, antimalarials and biologics were prescribed to 87.5%, 63.5, 54.2% and 1.0% of patients, respectively. The proportions of patients treated with corticosteroids (including oral and injectable forms) were not significantly different between subgroups (Table II). However, severe patients received a mean (SD) daily dose of prednisone 1.8 times higher than non-severe patients: 11.6 (7.5) *vs*. 6.5 (2.8) mg (p<0.001). Immunosuppressants (including oral and injectable forms) were prescribed twice as often to severe patients (p<0.001). Azathioprine and mycophenolate mofetil the two most used oral immunosuppressants were given to 28.1% and 20.8% of patients and represented 50% and 37% of the oral immunosuppressants, respectively. In contrast, antimalarials were prescribed twice as often to non-severe patients (p<0.001). Finally, antiosteoporotics were prescribed to 26.0% of patients (biphosphonates: 16.7%, calcium and/or vitamin D3: 9.4%).

Healthcare resources used by SLE patients

All patients were treated for SLE over the 2-year study period: 90.6% received corticosteroids, 70.8% immunosuppressants, 67.7% antimalarials, 20.8% NSAIDS, 4.2% biologics and 32.3% anti-osteoporosis drugs. Immunosuppressants were 1.8 times more prescribed to patients with severe disease (p<0.001). Corticosteroids tended also to be more likely prescribed to severe patients, but without significant difference. In contrast, antimalarials were 1.5 times more prescribed to non severe patients (p=0.009). Finally, antiosteoporotics were prescribed to 32.3% of patients, especially associated to high dose of corticosteroids.

All patients had at least one laboratory test over the study period (Table III). The median number of tests conducted annually (20.0) was 1.5 times higher in severe than in non-severe patients (p<0.001). An imaging test was prescribed to 64.6% of patients and a biopsy to almost 10% of them. Biopsies were more commonly prescribed to severe patients (p=0.031).

All patients visited a rheumatologist, 19.8% an ophthalmologist and 11.5% a neurologist. The proportion of specialist visits was not different between subgroups. Severe patients had a higher mean number of specialist visits than non-severe patients (p<0.001), mainly to the rheumatologist.

One third of patients (35.4%) were admitted to a hospital in inpatient stays at least once. Considering the average number of days spent in regular ward and day hospitalisation, patients were hospitalised two days annually (Table III).

Table III. Healthcare resources used.

Proportion of resources used over the 2-year study period	Severe patients (n=49)		Non-severe patients (n=47)		*p*-value
Medications	38	100%	48	100%	-
Antimalarials	27	55.1%	38	80.9%	0.009
Corticosteroids	47	95.9%	40	85.1%	0.088
Immunosuppressants	45	91.8%	23	48.9%	<0.001
Biologics	1	2.0%	3	6.4%	0.357
NAIDS	10	20.4%	10	21.3%	1.000
Anti-osteoporotic drugs	13	26.5%	18	38.3%	0.276
Tests	n	%	n	%	
Laboratory tests	49	100%	47	100%	-
Imaging tests	35	71.4%	27	57.4%	0.201
Biopsies	8	16.3%	1	2.1%	0.031
Specialist visits					
Rheumatologist	49	100%	47	100%	-
Ophthalmologist	7	14.3%	12	25.5%	0.205
Neurologist	8	16.3%	3	6.4%	0.200
Dermatologist	6	12.2%	3	6.4%	0.487
Hospitalisations					
At least one hospitalisation	24	49.0%	20	42.6%	0.546
Inpatient stays	19	38.8%	15	31.9%	0.527
Day hospitalisation / surgery	12	24.5%	7	14.9%	0.308
Emergency room visits	2	4.1%	3	6.4%	0.674

Number of resources used annually				
Tests				
Laboratory tests	Mean (SD)	30.1 (15.4)	18.6 (8.8)	<0.001
Median	25.4	16.6		
Min - Max	9.3 - 67.4	5.2 - 47.8		
Imaging tests	Mean (SD)	1.0 (1.0)	0.8 (0.9)	0.270
Median	0.7	0.5		
Min - Max	0 - 4.9	0 - 3.4		
*Biopsies	Mean (SD)	0.1 (0.2)	0.0 (0.1)	0.017
Min - Max	0 - 0.8	0 - 0.5		
Visits to the physician who managed patient's SLE	Mean (SD)	3.6 (1.2)	2.8 (1.0)	0.001
Median	3.4	2.8		
Min - Max	1.4 - 6.5	1.4 - 5.3		
Specialist visits	Mean (SD)	4.3 (1.6)	3.3 (1.4)	<0.001
Median	4.0	3.0		
Min - Max	1.9 - 9.9	1.7 - 8.2		
Rheumatologist	Mean (SD)	3.7 (2.8)	2.8 (1.0)	0.001
Median	3.4	2.6		
Min - Max	1.4 - 7.2	1.4 - 5.3		
*Ophthalmologist	Mean (SD)	0.1 (0.4)	0.2 (0.5)	0.166
Min - Max	0 - 2.0	0 - 2.1		
Hospitalisations				
*Inpatient stays	Mean (SD)	0.3 (0.4)	0.2 (0.3)	0.186
Min - Max	0 - 1.9	0 - 0.9		
*Day hospitalisation/surgery	Mean (SD)	0.6 (1.5)	0.1 (0.4)	0.659
Min - Max	0 - 6.8	0 - 2.0		
*Days in regular ward	Mean (SD)	1.3 (3.0)	1.9 (9.0)	0.186
Min - Max	0 - 13.0	0 - 60.3		

This table presents the proportion of patients and the categories of healthcare resources used over the study period, and the annual mean number of healthcare resources used per category.
*The median for these variables is 0 for the two groups of patients (with severe and non-severe disease).

Annual direct medical cost of care management of SLE patients

The median annual direct medical cost of SLE per patient was €2,101 in severe patients, 1.6 times higher than in non-severe ones (*vs.* €1,320; p=0.031). The minimum and maximum costs showed a wide range in both severe and non-severe cases. The mean annual cost per patient was slightly higher than the median cost (Table IV).

The ancillary study estimated the proportions of adult patients with active autoantibody positive disease at 55.6% with severe and 44.4% with non-severe disease. These results were used to weight the median annual direct cost which was adjusted to €1,754.

Distribution of the annual costs of healthcare resources used (Figure 1, Figure 2; Table V)

The costs of healthcare resources used annually are presented in median costs (Fig. 1) and in proportions of mean costs (Fig. 2).

Medications represented the main healthcare resources used (52.4% and 33.7% of the median annual total cost of severe and non-severe patients, respectively.

The median cost of medications was 2.5 times higher in severe than in non-severe patients (p=0.007), and was mainly due to the median cost of immunosuppressants (€685 *vs.* 0, p<0.001) and corticosteroid (€148 *vs.* 76, p<0.001) greater in severe than in non-severe patients.

The median costs of laboratory tests, specialists visits and biopsies/imaging tests were 1.7, 1.6 and 1.4 times significantly higher in severe than non-severe patients, respectively.

The cost of medications represented the highest proportion of the total cost of SLE patients (61.4%); and it was 1.5 times higher in severe than in non-severe patients (p=0.007).

The costs of immununosuppressants and of corticosteroids represented 35.3% and 8.6% of the total cost of SLE patients, respectively. Moreover, the costs of immununosuppressants and corticosteroids were 3 and 2.2 times higher, respectively, in severe than in non-severe patients (p<0.001 each).

The costs of laboratory tests and specialist visits was 1.6 and 1.5 times, respectively, higher in severe than in non-severe patients (p<0.001 each).

Annual number of flares

Since patients with active disease were selected at baseline, 70.8% flared at

Table IV. Annual direct medical cost of SLE by disease severity.

Annual direct medical cost of SLE (€)	Severe patients (n=49)	Non-severe patients (n=47)	*p*-value
Valid n	49	47	
Mean (SD)	2905 (2787)	2104 (2274)	0.031
Median	2101	1320	
Min - Max	365 - 15636	239 - 11310	
Q1-P25%	1106	546	
Q3-P75%	3637	3037	
95% CI Upper L	2104	1436	
95% CI Lower L	3705	2772	

Note: the annual direct cost of SLE was calculated as the overall direct medical cost per patient divided by per patient years of follow-up on an individual level.

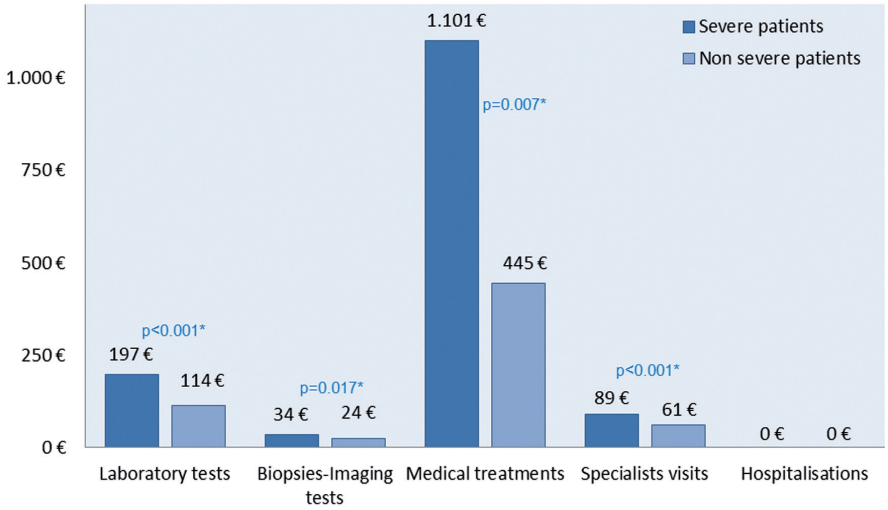

Fig. 1. Annual median direct costs of healthcare resource used per disease severity.

least once over the study period. Severe patients compared to non severe experienced 1.5 times more frequently flares (83.7% *vs* 57.4%, *p*=0.052), especially twice as often severe flares (51.0% *vs*. 23.4%, *p*=0.003).

The mean (SD) annual number of flares was 0.65 (0.60) flares, with severe flares more frequent in severe than in non-severe patients: 0.31 (0.34) *vs*. 0.21 (0.44), *p*=0.026. As a result, the majority of patients experienced annually on average one flare.

Moreover, severe patients compared to non-severe had more frequently severe flares which required a hospitalisation (0.25 *vs*. 0.15, *p*=0.004).

Costs predictors and cost drivers of SLE

Table VI presents the results of the univariate and multivariate regression analysis.

Factors related to annual direct costs assessed by a univariate analysis were introduced into the multivariate regression model. Low levels of C3 or C4 complement and the number and type of flares resulted to be independent predictors of direct medical costs of active SLE patients. Having low C3 or C4 complement levels increases the mean cost of €550 (*p*=0.011). Having a flare, mild/moderate or severe, increases the mean cost of €420 or €465, respectively, (*p*=0.02 each).

Discussion

The Italian data from the LUCIE study provides, for the first time in Italy, direct medical costs (medications, specialist visits, etc.) related to patients' clinical profiles. It also presents interesting clinical characteristics about patients presenting with active autoantibody positive disease, stratified by SLE severity.

The Italian LUCIE study confirms that younger age and male gender are associated with SLE disease severity, as described in other studies (20-23). Severe patients also had a higher score of disease activity and experienced more commonly severe flares, including those who required a hospitalisation. In contrast, organ damage was not significantly different between the two subgroups. This unexpected finding is probably due to the high frequency of damaged musculoskeletal systems which are considered within the spectrum of mild SLE manifestations.

Among the five countries investigated in the LUCIE study, the overall patients'

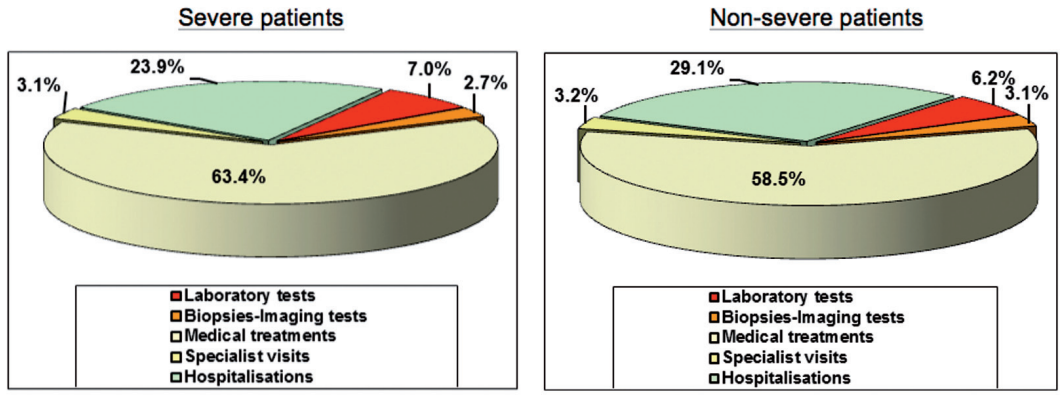

Fig. 2. Distribution of the annual mean medical direct cost per category of healthcare resource used.

Table V. Description of annual direct medical cost of SLE by disease severity.

Total cost		Severe patients (n=49) Mean 2905	% 100%	Non severe patients (n=47) Mean 2104	% 100%	*p*-value
Laboratory tests (€)						
	Any test(s)	202.9	7.0%	130.1	6.2%	<0.001
	Immunological tests	89.8	3.1%	63.4	3.0%	0.031
	Blood chemistry tests	77.6	2.7%	50.3	2.4%	<0.001
	Haematology tests	11.7	0.40%	8.2	0.39%	<0.001
	Other biological test	23.7	0.82%	8.1	0.38%	<0.001
Biopsies and imaging tests (€)						
	Any test(s)	77.6	2.7%	64.9	3.08%	0.159
	Biopsies	7.7	0.26%	0.75	0.04%	0.017
	Imaging test	69.9	2.41%	64.2	3.05%	0.281
Medications (€)						
	Any medication(s)	1842	63.4%	1231.0	58.5%	0.007
	NSAIDS	5.4	0.19%	7.6	0.36%	0.735
	Corticosteroids	294.9	10.2%	136.2	6.5%	<0.001
	Antimalarials	52.4	1.8%	74.5	3.5%	0.031
	Immunosuppressants	1316.6	45.3%	437.2	20.8%	<0.001
	Biological drugs	48.1	1.7%	280.4	13.3%	0.290
	Anti-osteoporosis drugs	124.7	4.3%	295.0	14.0%	0.077
	Other treatments	0	0%	0	0%	-
Specialist visits (€)						
	Any visit(s)	89.1	3.1%	67.1	3.2%	<0.001
	Dermatologist	1.1	0.04%	0.62	0.03%	0.335
	Ophthalmologist	2.6	0.09%	4.4	0.21%	0.166
	Rheumatologist	76.2	2.62%	57.2	2.7%	<0.001
	Pulmonologist	1.5	0.05%	1.1	0.05%	0.280
	Cardiologist	1.1	0.04%	0.4	0.02%	0.392
	Neurologist	2.3	0.08%	0.67	0.03%	0.154
	Nephrologist	0.82	0.03%	0.41	0.02%	0.336
	Psychiatrist	0	0%	0	0%	-
	Internist (internal medicine)	0	0%	0	0%	-
	Surgical visit(s)	0.41	0.01%	0.88	0.04%	0.373
	Other visits	3.1	0.11%	1.32	0.06%	0.117
Hospitalisations (€)						
	Any visit	693.0	23.9%	611.2	29.1%	0.721
	Day hospitalisation/day surgery	118.3	4.1%	50.3	2.4%	0.089
	Emergency room visits (€)	4.9	0.17%	7.6	0.36%	0.614
	Inpatient stays (€)	569.8	19.6%	553.1	26.3%	0.759
	Rehabilitation stays (€)	0	0%	0.21	0.01%	0.307

Note: the percentage is calculated as mean cost of each health resource with respect to global costs in each severity group and for overall sample.

profile seemed to be 'less' active and 'less' severe in the Italian population (16). The proportion of chronic active patients (17%), of patients who experienced at least one flare over the study period (70.8%), the annual number of flare (0.65), the average score of disease activity (6.3) and of organ damage (0.4) at baseline were the lowest in Italy.

Differences in disease activity observed in Italy can be partly explained by the low proportion of non-Caucasians patients (7.3%) compared to the UK (45.3%) and France (not collected). In fact, African descendents/African American patients, Asians and Latin/Hispanic American are known to have a more active and severe disease than Caucasians (24).

Moreover, the type of patients' recruitment was different across countries. Rheumatologists are the SLE primary care managers in Italy, Germany and the UK; in contrast with internists in France and Spain, who usually follow-up a wide range of manifestations and organs involvements, reflecting patients with a most severe disease. Patients with probably more active and/or damaged forms were included in the study (while hospitalised) in Spain, (with SLE nephritis) in France, and (elder people) in Germany.

The LUCIE study clearly shows that physicians follow SLE treatments recommendations. Corticosteroids were prescribed to almost all patients (87.5%), nevertheless the dose was adapted to disease severity. Prednisone, the most used oral corticosteroid, was twice as often prescribed to severe than non-severe patients. Immunosuppressants, as expected, were mainly prescribed to severe patients, for treating the most severe forms and relapses in disease activity. Mycofenolate mofetil, the most used immunosuppressant, was also mainly prescribed to severe patients. The use of this most expensive immunosuppressant has increased in the last few years (25, 26). In contrast, antimalarials were more commonly prescribed to non-severe patients. Actually, they should be used in the treatment of both severe and non-severe manifestations as adjunctive therapies as pointed out by European and American recommendations (27, 28). Finally, anti-osteoporotic drugs were used only by one third of patients. More attention should be reserved to the crucial aspect of preventing bone fractures in patients treated with costicosteroids. In addition, low vitamin D3 serum levels were shown in SLE patients compared to healthy subjects (29) and were associated with active disease (30) and antiphospholipid antibody syndrome (31). Thus SLE patients should be routinely supplemented with vitamin D (32).

The annual total direct medical cost of SLE is related to three main factors: medications, low C3 or C4 complement levels and flares occurrence. Medications, especially immunosuppressant drugs, were the major cost drivers since they represented the large majority of the total cost of SLE. Biologics are now widely used and will be much more prescribed in the next years. Belimumab has recently been approved for SLE (11), and other biologics are being developed or used as off-label treatments (9). Flares, especially severe

Table VI. Results of the multivariate regression models.

		Univariate analysis *p*-value	Multivariate analysis			
			Beta coefficient	Standard error	*p*-value	R^2
SLE duration		0.046	-	-	-	
Disease severity		0.028	-	-	-	
Disease course (chronic active *vs.* relapsing-remitting)		0.281	-	-	-	
Renal domain involved		0.106	-	-	-	
Haematology domain involved		0.492	-	-	-	
SELENA-SLEDAI score		0.013	-	-	-	
SLICC/ACR score		0.138	-	-	-	
Annual mean number of flares		0.002	-	-	-	
Annual mean number of mild flares		0.173	-	-	-	
Annual mean number of severe flares		0.001	-	-	-	
Intercept			6.55	0.20	<0.0001	0.27
Annual number of mild flares:	1 *vs.* 0	0.049	0.47	0.20	0.023	Amount: €420
	2 *vs.* 0	0.551	0.33	0.30	0.282	–
Annual number of severe flares:	1 *vs.* 0	<0.001	0.51	0.21	0.020	€465
	2 *vs.* 0	0.070	0.81	0.45	0.077	–
Low complement levels: C3 or C4		<0.001	0.58	0.22	0.011	€550

This table presents the results of the multivariate regression model.
First step: each independant variables were tested in univariate analysis.
Second step: the significant variables were then included into the multivariate regression model.
Note: the variables related to flares showed a colinearity; thus only those including the number and type of flares were kept and included in the model presented here.

Table VII. Summary of the patients' clinical profile and mean annual cost of SLE patients for the 5 countries involved in the LUCIE study.

	Italy	France	UK	Germany	Spain
Chronic active patients	17.0%	26.9%	33.7%	33.8%	44.0%
SELENA-SLEDAI score (mean)	6.3	7.7	7.7	9.8	10.2
SLICC/ACR index score (mean)	0.4	0.8	0.8	1.6	0.7
At least a flare over study period	70.8%	96.8%	91.9%	89.6%	90.7%
Number of flares per year (mean)	0.65	1.10	1.25	1.03	1.11
Median annual cost of SLE	€1,862	€2,695	€3,329	€1,930	€2,615
Mean annual total cost of SLE	€2,513	€4,116	€3,766	€3,452	€4,833
Mean annual cost of medications	€1,543	€2,542	€1,506	€2,349	€1,506
% of total cost of SLE	61.4%	61.8%	40.0%	68.1%	29.6%

flares, and low C3 or C4 complement levels, clinical manifestations of disease activity, were identified as major cost predictors. These cost drivers and predictors are part of those described in other studies, such as younger age (12, 33), high disease activity at onset (12, 33, 34), flares, particularly involving major organs (34) or disease severity, mainly active renal (35) and neuropsychiatric (36) involvement.

The cost of SLE care in Italy (mean: €2,513 and median: €1,862), was the lowest among the five countries involved in the LUCIE study (Table VII) (16). Since the cost of SLE is being described for the first time in Italy, it cannot be compared to other Italian studies. However, the mean annual costs of SLE assessed in the UK (14, 16) and Germany (16) were consistent with those described in the two available studies conducted in Europe, which, actualised in €2009, was estimated at €3,421 in the UK (12) and €3,636 in Germany (13). Nevertheless, the five countries have common findings: the cost of SLE care management and the cost of medications were significantly higher in severe than non-severe patients. Notably, the costs of medications, which were similar in Italy, UK and Spain, were higher in Germany and in France (Table VII) (16).

Differences between countries could be explained by clinical and medico-economic aspects. Since in Italy the overall patients' profile seemed to be 'less' active, medical resources needed for patients' care management were therefore lower in this country.

Moreover, the healthcare systems are different in the five countries. The average costs of SLE patients were the highest in Spain and France, the two countries where SLE patients are mainly followed-up in internal medicine departments which probably manage patients with more complex and severe manifestations. Nevertheless, in all countries, physicians send the patient to other specialist when needed (ophthalmologist, nephrologist, etc.), according to a coordinated healthcare pathway.

Eventually, the average relative unit costs of some resources (*e.g.* immunosuppressants, specialist visits) are less expensive in Italy. As an example, the unit cost of oral mycophenolate was evaluated at €3.58/g in Italy (it ranged from €3.97 to €6.91 in the other countries).

The Italian LUCIE study has some limitations. One of the four participating centres included 52% of study population to compensate for the withdrawal of another one. This 'centre effect' may have lead to a more homogeneous study population. Nevertheless, the total number of patients per disease severity was balanced within centres and at country level. Severe and non-severe patients were stratified as 50:50 to have enough power for statistical analysis by subgroups. Due to the retrospective nature of the study, direct medical costs may have been underestimated since some clinical/healthcare consumption was not recorded in medical files (*e.g.* non-specialist visits, mainly to general practitioners, SLE comorbidities treatments, antibiotics). Disease activity, organ damage and disease severity were assessed only at baseline, thus the potential disease progression and damage accrual could not be evaluated over the two-year study period. Finally, since there is no accepted definition of

a lupus flare, specific criteria have been suggested to identify a flare and determine its start. However, the estimated mean number of flares was comparable to other studies (34, 36).

In conclusion, the LUCIE study provides insights about SLE clinical profiles, and for the first time, the direct cost of SLE care management in Italy. This cost is high, but it is less expensive than other chronic diseases such as multiple sclerosis which cost is 2.5–5 times higher (37). The results also confirmed the importance of preventing complications and limiting disease activity and progression. In fact a remittent disease over long time periods remains alternatively active over time in many patients (38). The use of antimalarials to prevent flare occurrence, even in severe patients, and the use of anti-osteoporotics and Vitamin D in patients treated with corticosteroids to prevent bone fractures could be increased to improve the disease long term prognosis (39, 40).

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