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Lupus. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Lupus. 2018 October ; 27(11): 1799–1809. doi:10.1177/0961203318790675.

Health Care Resource Utilization and Costs Associated with Long-Term Corticosteroid Exposure in Patients with Systemic Lupus Erythematosus (SLE)

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Abstract

Objective: Evaluate the association between exposure to oral corticosteroids (CSs) and future healthcare resource utilization (HCRU) and costs for patients with systemic lupus erythematosus (SLE).

Methods: Adults diagnosed with SLE (index date) between January 1, 2008 and June 30, 2013 and naive to oral CSs with continuous health plan enrollment for ≥6 months pre- and ≥5 years post-index were identified from a large health plan claims database. Per-patient monthly average daily dose (ADD) of oral CSs (prednisone or its equivalent) was calculated for the first 2 years post-index to categorize patients into 4 steroid exposure cohorts: low (≤5 mg/day), medium (6–20 mg/day), high (>20 mg/day) and no-steroids. Differences in HCRU and total healthcare costs during the third year post-index across CS exposure cohorts were modeled with adjustment for baseline characteristics.

Results: Study included 18,618 SLE patients (163 high-dose, 1,127 medium-dose, 6,717 low-dose, and 10,611 no-steroids). Compared to low-dose CS users, high-dose CS users were more likely to have emergency room visits (39.3% vs. 29.7%; p=0.0085) and to be hospitalized (21.5% vs. 12.3%; p=0.0005). After adjustment for baseline characteristics, they also had significantly greater average annual total healthcare costs ($60,366 vs. $18,777; p<0.0001). A one milligram increase in CS average daily dose was associated with 1.07 times the average annual costs after adjusting for baseline characteristics (p<0.0001).

Conclusion: Long-term high-dose oral CS use was associated with significantly greater future HCRU and costs. Judicious reduction in daily steroid dose may decrease the imminent economic burden associated with high-dose steroid use in SLE.

Keywords

Lupus; SLE; Corticosteroids; Costs; Resource Utilization; Burden

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a serious chronic autoimmune disease characterized by widespread inflammation in multiple organs.[1,2] It occurs primarily in young women of child-bearing age.[1,3] According to estimates of the Lupus Foundation of America, 1.5 million Americans have a form of lupus and more than 16,000 new cases are reported every year.[4] SLE is associated with compromised health-related quality of life (HRQoL) and significant economic burden, with mean annual direct costs reported to range from $13,735 to $20,926 per person in the United States (US) (adjusted to 2009 US dollars).[5,6,7,8,9,10,11,12,13,14] Mean annual medical costs for patients with SLE are reported to be 3 to 4 times greater compared with those for people without SLE.[15]

Current treatment options manage symptoms of disease and reduce the number and severity of flares, with corticosteroids (CSs) often being the cornerstones of treatment.[16,17,18,19] Despite this, few studies have evaluated the impact of CS dose on healthcare resource utilization (HCRU) and costs among SLE patients in the US. They have reported greater doses of CSs to be associated with increased risk/incidence of various CS-associated adverse events and greater annual HCRU and costs.[20,21,22,23,24] Although the clinical burden and toxicity of CSs are well-established in the literature, none of these studies have evaluated the HCRU and costs among SLE patients *newly* initiating oral CS therapy and receiving long-term high-dose/medium-dose/no CSs vs. low-dose oral CSs. Published large administrative database studies that evaluated CS-associated HCRU and costs in SLE also used relatively older data[21,23], while US payers are interested in recent data. As CSs are commonly prescribed in SLE patients and many patients take them chronically, it is important to generate evidence on the current clinical and economic burden associated with long-term CS use. Thus, the goal of this study was to evaluate the association between exposure to oral CSs measured over 24 months and future HCRU and costs in commercially insured SLE patients newly initiating oral CS treatment in the US.

PATIENTS AND METHODS

DATA SOURCE

This observational, retrospective cohort study was conducted using the IQVIA PharMetrics Plus (PMTX+) Health Plan Claims Database from July 1, 2007, to June 30, 2016. This database comprises adjudicated medical and pharmacy claims for more than 150 million unique health plan members across the US, providing a diverse representation of geography, employers, payers and providers. Data elements include inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, pharmacy and medical benefit (co-pay, deductible) information, inpatient stay and provider details, demographic variables, product type, payer type, and start and stop dates of health-plan enrollment. Amounts charged by the providers and allowed and paid by the health plans are available for all services rendered. The database is nationally representative of the US commercially insured population in terms by age and sex. Patients in each three-digit zip code and every metropolitan statistical area of the US are included, with data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies. All data

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are compliant with the Health Insurance Portability and Accountability Act (HIPAA) to protect patients' privacy.

SAMPLE SELECTION

Patients aged ≥18 years with ≥2 non–same-day medical claims with a diagnosis of SLE (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 710.0x) between January 1, 2008, and June 30, 2013 (selection period) were identified in the database. The date of the first observed SLE diagnosis code (≥2 non-same-day medical claims with a diagnosis of SLE [ICD-9 710.0x] were required) was defined as the index date (prevalent SLE population). For inclusion, patients needed to have continuous health plan enrollment for ≥180 days immediately preceding the index date (pre-index period) and ≥1,080 days immediately following the index date (post-index period). Patients were excluded from the study if they had ≥1 pharmacy claim for oral steroids during the 180-day pre-index period; were aged ≥65 years and not covered by Medicare Risk, had Medicare Cost coverage or State Children's Health Insurance Program (SCHIP); or had data quality issues (missing drug quantity information or invalid year of birth, sex, or health plan enrollment dates).

DEFINING CORTICOSTEROID EXPOSURE GROUPS

The first 2 years of the post-index period were used to create oral CS exposure groups for comparison (exposure period), while the third year of the post-index period was used to evaluate outcome measures. Three of the four exposure groups of interest were based on evidence of ≥1 pharmacy claim for an oral CS (betamethasone, budesonide, cortisone acetate, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisone or triamcinolone) during the exposure period and following their first SLE diagnosis. The first oral CS prescription/administration was defined as the patient's treatment index date. All patients with no evidence of oral CSs in the exposure period formed the fourth, "no-steroid user" cohort and retained their SLE diagnosis-based index dates.

To account for both length of exposure as well as variable dosing, patients' average daily dose (ADD) of prednisone (the most commonly used oral CS in SLE patients) for each of the first 24 months post-index was calculated using the following formula derived from pharmacy claims: (Strength x Quantity) / Days Supply.

The per-patient average monthly ADD was then calculated for the 24-month period, and the resultant values were used to categorize patients into three mutually exclusive exposure groups (based on literature review and inputs from clinical experts):

1) "Low-dose", defined as ≤5mg/day
2) "Medium-dose", defined as 6–20mg/day
3) "High-dose", defined as >20mg/day

ADDs of other oral CSs (e.g., methylprednisolone) were converted into the prednisone equivalent.[25]

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STUDY MEASURES

All-cause HCRU and all-cause healthcare costs were evaluated in the post-index period during the third year. HCRU included the mutually exclusive categories of pharmacy services (Rx), emergency room (ER) visits, outpatient (OP) visits and inpatient (IP) visits. Costs were assessed for each of these HCRU services. Only direct health care costs for services covered by the patient's insurance benefit were reported, using allowed amounts on the claims, which represented the contracted reimbursable amount for covered medical services or supplies that the health plan agrees to pay to service providers. Costs were converted to 2016 US dollar using the medical component of the Consumer Price Index.

Patient demographics and baseline clinical characteristics were identified during the pre-index period. These included age at index date, sex, health plan type, payer type, region, index year, physician specialty (that recorded the SLE diagnosis), rheumatology visit, primary care physician (PCP) visit, hematology visit, nephrology visit, Charlson Comorbidity Index (CCI) score, comorbidities, concomitant medications (non-steroidal anti-inflammatory drugs [NSAIDs], anti-malarials, and immunosuppressants [e.g., cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus), total medical costs and total pharmacy costs.

STATISTICAL ANALYSES

For categorical measures, data were reported as the frequency (number of cases [N]) and percentage (%) of total patients observed in each category. For continuous variables, data were reported as the mean, standard deviation (SD), and median. Differences in the distribution of these variables were tested for statistical significance using the chi-squared test for categorical variables and the non-parametric Wilcoxon rank-sum test for continuous variables. A p-value of ≤ 0.05 was considered statistically significant. Generalized linear modelling (with a log link function and gamma error term distribution) was used to evaluate differences in total healthcare costs during the third year post-index among CS exposure cohorts. Models were adjusted for age, gender, CCI score, cardiovascular disease (e.g., acute myocardial infarction, coronary atherosclerosis, aneurysm, pulmonary embolism, pericarditis, valve disorders, cardiomyopathy, tachycardia, atrial fibrillation, congestive heart failure, embolism) renal disease (e.g., glomerulonephritis, nephrotic syndrome, nephritis, nephropathy, acute kidney failure, chronic kidney disease, end state renal disease, renal failure, renal sclerosis), pre-index total medical costs and pre-index use of prescription NSAIDs and anti-malarial agents. These specific variables were selected for adjustment as they confound the association between steroid dose and HCRU/costs; furthermore, they have been previously demonstrated to be associated with HCRU and costs in SLE.[21,23]

RESULTS

STUDY ATTRITION

In total, 109,817 patients were initially identified as having evidence of SLE, of whom 91,199 (83%) were excluded for the reasons listed in Figure 1. The remaining 18,618 patients included 163 high-dose oral CS patients, 1,127 medium-dose oral CS patients, 6,717 low-dose oral CS patients, and 10,611 no-steroid use patients (Table 1).

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LOW-DOSE ORAL CSS VS. HIGH- AND MEDIUM-DOSE ORAL CSS

Baseline characteristics—Compared with patients receiving low-dose CSs, patients receiving high-dose CSs were younger (46 vs. 43 years; p=0.0002), had a higher risk of renal disease (4.0% vs. 12.9%; p<0.0001) and had greater mean pre-index total medical costs ($5,997 vs. $11,977; p=0.0013). Compared with patients receiving low-dose CSs, patients receiving medium-dose CSs were also younger (46 vs. 44 years; p<0.0001), had a higher risk of renal disease (4.0% vs. 10.2%; p<0.0001) and had higher mean pre-index total medical costs ($5,997 vs. $9,467; p<0.0001). Table 1 provides additional details on the baseline characteristics of patients eligible for inclusion into our study.

Unadjusted HCRU and costs in the third year post-index—A significantly greater percentage of patients receiving high-dose oral CS used ER services (39.3% vs. 29.7%; p=0.0085) and had ≥1 IP hospitalization (21.5% vs. 12.3%; p=0.0005) in the third year post-index compared to those receiving low-dose oral CS. Mean healthcare utilization (Rx, ER, OP and IP services) and mean all-cause total costs ($60,366 vs. $18,777; p<0.0001) in the third year post-index were significantly greater for patients receiving high-dose oral CS. Table 2 and Figure 2 provide additional details.

A significantly greater percentage of patients receiving medium-dose oral CS used ER services (33.5% vs. 29.7%; p=0.0097) and had ≥1 IP hospitalization (17.6% vs. 12.3%; p<0.0001) in the third year post-index compared to those receiving low-dose oral CS. Mean healthcare utilization (Rx, ER, OP and IP services) and mean all-cause total costs ($31,095 vs. $18,777; p<0.0001) in the third year post-index were significantly greater for patients receiving medium-dose oral CS. Table 2 and Figure 2 provide additional details.

Multivariate models—In multivariate adjusted analysis, patients in the high-dose and medium-dose groups had 2.8 times (cost ratio [CR]: 2.80, 95% confidence interval [CI]: 2.290–3.420) and 1.7 times (CR: 1.71, 95% CI: 1.571–1.850) the average annual all-cause healthcare costs, respectively, compared with those in the low-dose oral CSs group (Table 3). In a separate multivariate adjusted analysis, a 1-mg/day increase in steroid ADD increased the total all-cause healthcare costs by 1.07 times in the third year post-index (CR: 1.07, 95% CI: 1.062–1.074; p<0.0001) (Figure 3).

LOW-DOSE ORAL CSS VS. NO-STEROIDS

Baseline characteristics—Compared with patients receiving low-dose CSs, patients in the no-steroids group were older (46 vs. 47 years; p=0.0003) with a lower proportion of patients having CV disease (13.5% vs. 10.8%; p<0.0001) and infection (43.9% vs. 36.1%; p<0.0001) in the 6-month pre-index period. Mean pre-index total medical and pharmacy costs were significantly lower for patients in the no-steroids group compared to those receiving low-dose CS ($5,195 vs. $5,997; p=0.0206 and $1,207 vs. $1,620; p<0.0001, respectively). Table 1 provides additional details.

Unadjusted HCRU and costs in the third year post-index—A significantly lower percentage of patients in the no-steroids groups used ER services (22.4% vs. 29.7%; p<0.0001) and had ≥1 IP hospitalization (9.5% vs. 12.3%; p<0.0001) in the third year post-

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index compared to those receiving low-dose oral CS. Mean healthcare utilization (Rx, ER, OP and IP services) and mean all-cause total costs ($13,632 vs. $18,777; p<0.0001) in the third year post-index were significantly lower for patients in the no-steroids group. Table 2 and Figure 2 provide additional details.

Multivariate model—In multivariate adjusted analysis, patients in the no-steroids group had 0.7 times (CR: 0.72, 95% CI: 0.697–0.754) the average annual all-cause healthcare costs compared with those in the low-dose oral CSs group (Table 3).

DISCUSSION

In this study, patients in the high-dose and medium-dose oral CS groups had significantly greater (2.8 times and 1.7 times, respectively) average annual total healthcare costs compared with patients in the low-dose group. Patients in the no-steroids group had significantly lower (0.7 times) average annual total healthcare costs compared with patients in the low-dose group. Although previous studies have evaluated the economic burden of SLE associated with the use of oral CSs[7,8,10,11,21], none of these studies have evaluated the impact of *long-term* exposure to CSs in SLE patients newly initiating oral CS treatment. Chen et al.[23] conducted a cross-sectional study among adult SLE patients using a large US insurance claims database and associated oral GC use with greater annual HCRU and costs. Mean total healthcare costs during a 1-year follow-up period were reported to double from patients receiving low-dose GC to patients receiving greater-dose GC.[23] Compared to this study, our study included SLE patients new to oral CSs and evaluated the impact of long-term exposure to CSs on HCRU and costs (i.e. the first 2 years after SLE diagnosis were used to create CS exposure groups of interest and the third year post-index was used to evaluate the outcomes of interest). We also used different definitions that were agreed upon by rheumatology experts to identify high, medium and low-dose steroid use.

In our study sample, significantly greater percentage of patients receiving high-dose and medium-dose oral CSs consulted a nephrologist as their prescribing physician specialty, had renal disease, had greater number of nephrology visits and had significantly greater total medical costs in the pre-index period compared with those receiving low-dose oral CSs. Patients in the non-steroid group had significantly lower rheumatology visits, PCP visits and total medical and pharmacy costs in the pre-index period compared with those receiving low-dose oral CSs. Therefore, it was required to adjust for baseline characteristics, including pre-index medical costs and the CCI, in order to account for the covariate imbalance that exists when evaluating the association between steroid dose and HCRU/costs.

Compared to patients receiving low-dose oral CSs, a significantly greater percentage of patients receiving high-dose and medium-dose oral CSs used ER services and had ≥1 IP hospitalization with a longer mean length of stay in the third year post-index. On the other hand, a significantly lower percentage of patients in the non-steroid group used ER services, had ≥1 IP hospitalization and had a shorter mean length of hospital stay compared with those receiving low-dose oral CSs. Patients receiving CSs may need more regular monitoring, which may result in increased HCRU.[20,26] More frequent ER visits and

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hospitalizations for patients who received greater CS doses may be attributed to greater disease severity, flares, worst general health status or treatment of adverse events.[19,27,28]

The International Task Force for SLE recommends prescription of the lowest GC dose needed for disease control and to withdraw GC completely, if possible.[29] In addition, duration of exposure to CSs should be minimized.[30] Pre-existing comorbidities that may increase the risk of experiencing CS-related adverse events in the future should be evaluated prior to initiating CS therapy.[30] These actions may help reduce complications and economic burden associated with CS use for SLE patients and may improve HRQoL.[31] Steroid-sparing agents can accelerate the process of decreasing steroid requirements in SLE patients, yet tolerable and effective treatment options are limited. Treatment options that will help decrease CS use in SLE patients and improve their clinical, economic, and HRQoL outcomes are needed.

Antimalarial use is lower in our cohort (22.1%−33.4%) in comparison to other cohorts. For example, between 61–83% of SLE patients in the Lupus in Minorities, Nature versus Nurture (LUMINA) cohort reported hydroxychloroquine use.[32] In a Medicaid administrative database study of patients with SLE receiving immunosuppressive therapy (i.e., MMF, azathioprine or cyclophosphamide), 30.1%−54.4% were on hydroxychloroquine.[33] The differences in antimalarial treatment utilization among the different cohorts are likely due to differences in patient samples included in the studies. The LUMINA cohort was primarily recruited from rheumatology clinics and had to meet the American College of Rheumatology definition of SLE for inclusion. In contrast, we identified SLE patients based on a previously validated method using provider-reported ICD-9 diagnosis codes. The SLE Medicaid population also has a very different sociodemographic (including age, income, race/ethnicity) profile than our cohort. For instance, the mean age of our study cohort is 45 while the mean age of the Medicaid cohort is 35.

This study had several limitations. First, administrative claims data sets are not designed for the primary purpose of conducting research. The internal validity is typically not sufficient to make positive inferences of cause and effect. Second, the analytic focus was on patients who met the continuous observation criteria (6 months pre-index and 36 months post-index), with a potential to eliminate patients who may have different treatment patterns coincident with observation patterns. Results may not be generalizable to those without consistent access to care, for instance. Third, patients selected for one particular treatment rather than another may have very different characteristics. Some of these differences were measured in our study (such as age and sex) but some are not measurable or not available in the dataset (e.g., patient preferences). Fourth, treatments may not be captured within the data-set and there may be incomplete encounter histories for patients selected for this study. Fifth, medical billing codes used to indicate diagnoses and procedures are subject to non-clinical influences. Finally, although adjustment for relevant baseline characteristics in the multivariate modelling was done, the opportunity for residual confounding remains.

In conclusion, in a contemporary cohort of SLE patients new to oral CSs, high- and medium-dose CS use was associated with significantly greater future healthcare utilization and costs relative to low-dose steroid use, after adjustment for baseline demographic and

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clinical characteristics. No-steroid use was associated with significantly lower future healthcare utilization and costs relative to low-dose steroid use. Patients with SLE receiving CSs require greater resource use for disease and medication management. Minimizing the daily steroid use of SLE patients while concomitantly controlling their disease activity may reduce the looming economic burden associated with CS use.

Acknowledgments

Grant(s) or other financial supporter(s) of the study: IQVIA received research funding from AstraZeneca. EV received fees for consulting services related to the design and conduct of the study.

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Summary

- This is the largest US claims database study evaluating the healthcare resource utilization (HCRU) and costs associated with long-term exposure to different doses of oral corticosteroids (CSs) for adult patients with systemic lupus erythematosus (SLE) newly initiating oral CSs.
- High-dose (>20mg/day) and medium-dose (6–20 mg/day) oral CS use was associated with significantly greater future healthcare costs relative to low-dose (≤5 mg/day) oral CS use.
- No-steroid use was associated with significantly lower future healthcare costs relative to low-dose oral CS use.
- A one milligram increase in CS average daily dose was associated with 1.07 times the average annual costs after adjusting for baseline characteristics ($p<0.0001$).

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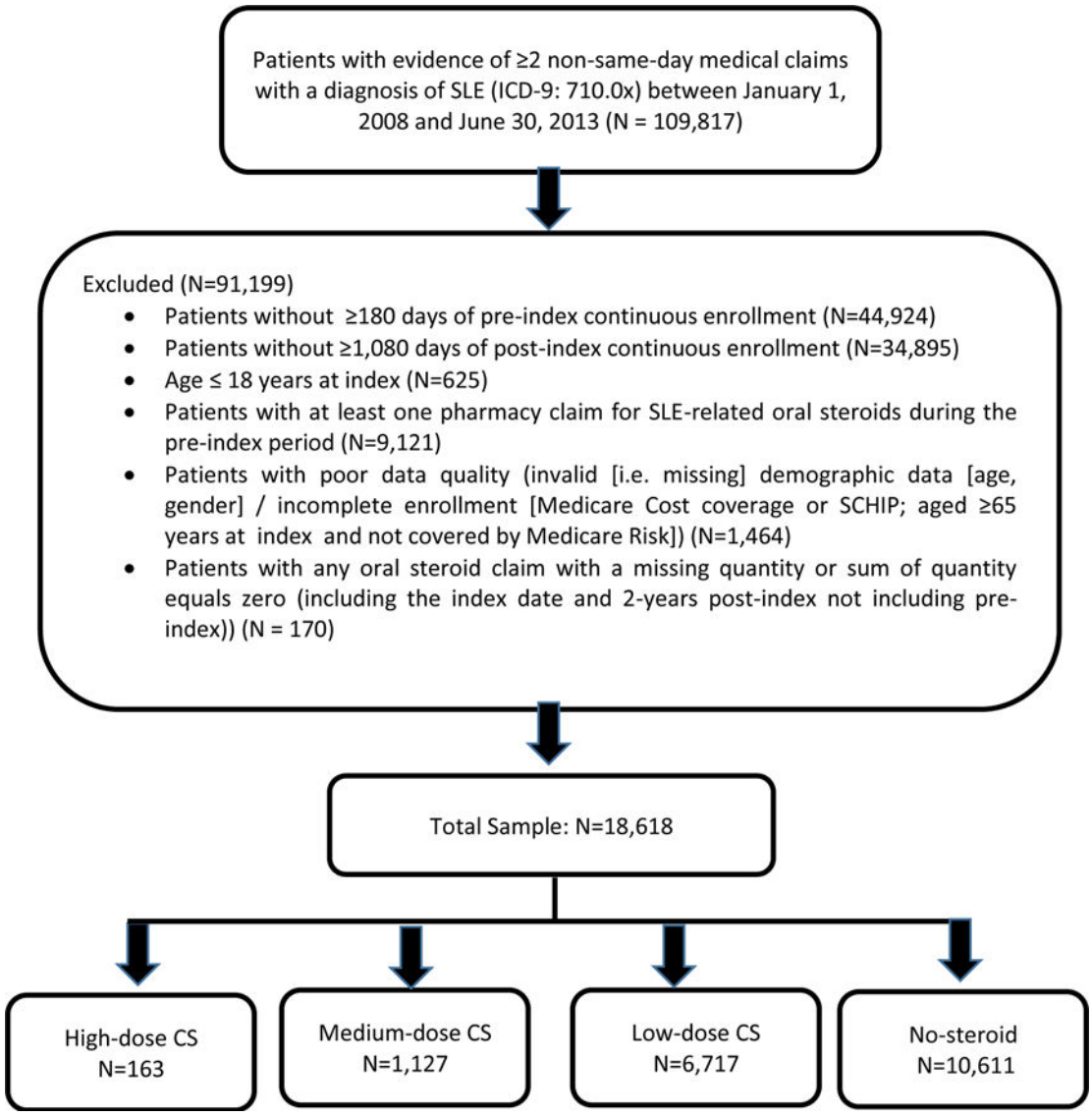

Figure 1:
Sample Selection

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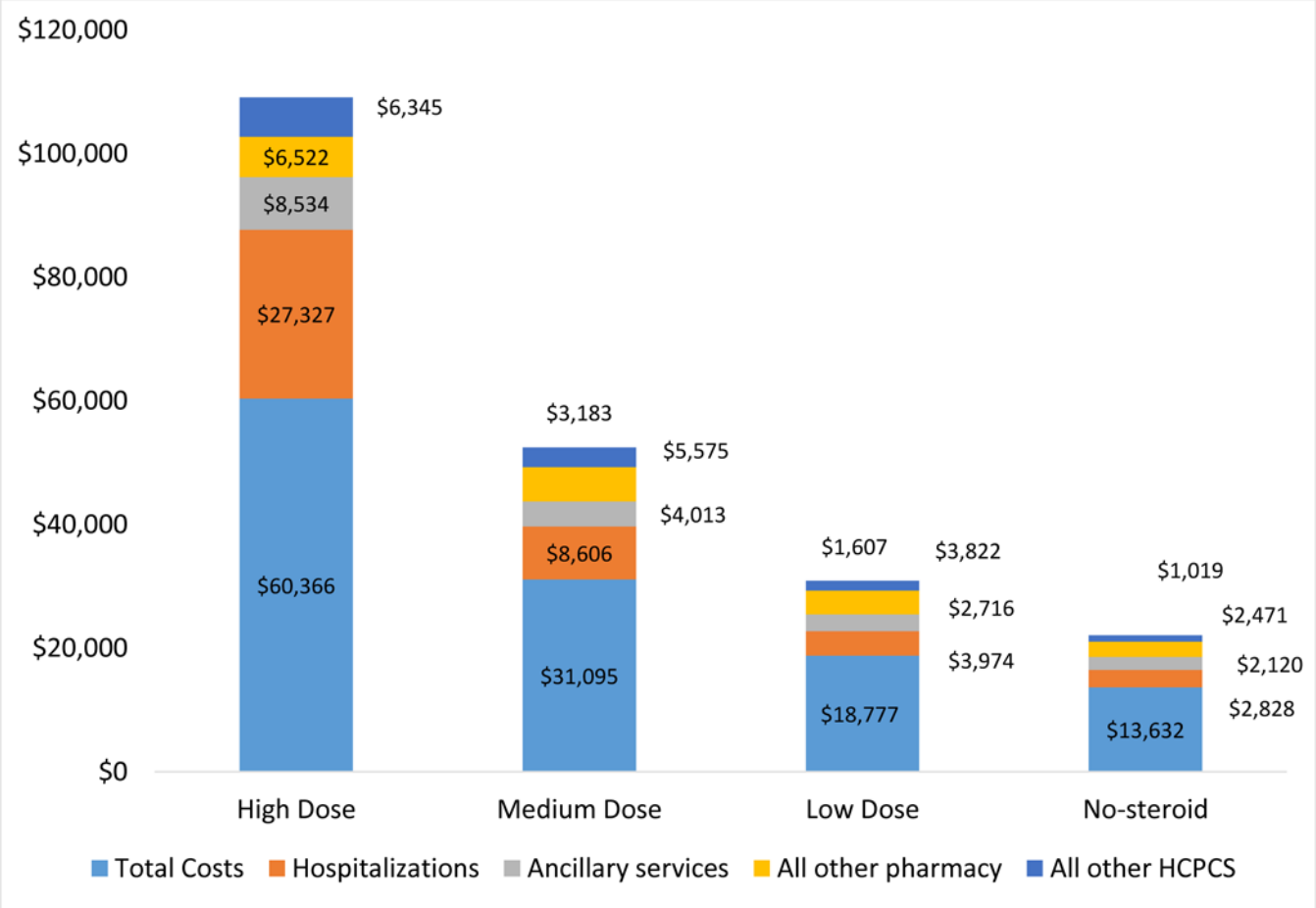

Figure 2.

Healthcare component costs among patients with SLE, by CS dose exposure category (third year of follow up)

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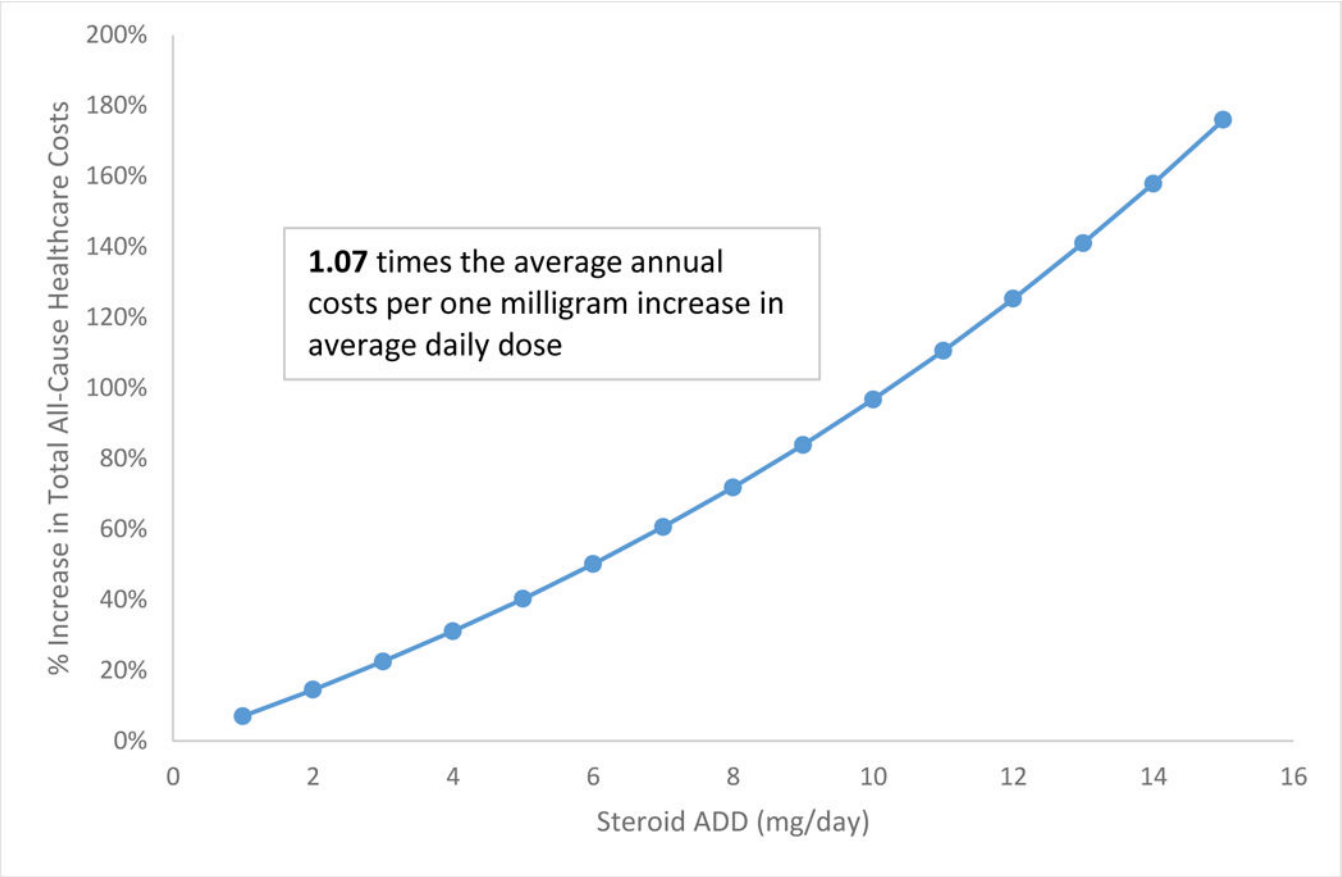

Figure 3:
Total all-cause healthcare costs with one mg/day increase in steroid average daily dose

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Table 1.

Baseline characteristics of the study sample

Patient cohort	High Dose CS (HD) (N = 163)		Medium Dose CS (MD) (N = 1,127)		Low Dose CS (LD) (N = 6,717)		No-steroid Dose (NS) (N = 10,611)		p-value (HD vs. LD)	p-value (MD vs. LD)	p-value (NS vs. LD)
Age Group (n, %)											
18–34 years	46	28.2%	249	22.1%	978	14.6%	1,505	14.2%	†	*	†
35–44 years	35	21.5%	283	25.1%	1,648	24.5%	2,408	22.7%			
45–54 years	47	28.8%	369	32.7%	2,426	36.1%	3,764	35.5%			
55–64 years	34	20.9%	221	19.6%	1,642	24.4%	2,890	27.2%			
65+ years	1	0.6%	5	0.4%	23	0.3%	44	0.4%			
Age (years)											
Mean ± SD	43.3 ± 12.4		44.1 ± 11.4		46.3 ± 10.5		46.9 ± 10.7		†	*	†
Gender, (n, %) Female	143	87.7%	987	87.6%	6,190	92.2%	9,523	89.7%	†	*	*
Health Plan Type (n, %)											
Consumer-directed	0	0.0%	9	0.8%	23	0.3%	50	0.5%		†	*
HMO	24	14.7%	193	17.1%	925	13.8%	1,797	16.9%			
Indemnity	5	3.1%	31	2.8%	165	2.5%	356	3.4%			
POS	10	6.1%	53	4.7%	239	3.6%	455	4.3%			
PPO	121	74.2%	833	73.9%	5,300	78.9%	7,837	73.9%			
Other/Unknown	3	1.8%	8	0.7%	65	1.0%	116	1.1%			
Payer Type (n, %)											
Commercial	89	54.6%	647	57.4%	3,886	57.9%	6,064	57.1%			†
Medicaid	9	5.5%	57	5.1%	264	3.9%	565	5.3%			
Medicare	1	0.6%	8	0.7%	36	0.5%	60	0.6%			
Self-insured	61	37.4%	410	36.4%	2,496	37.2%	3,845	36.2%			
Other/Unknown	3	1.8%	5	0.4%	35	0.5%	77	0.7%			
Region (n, %)											
Northeast	39	23.9%	284	25.2%	1,576	23.5%	3,018	28.4%		†	*
Midwest	48	29.4%	279	24.8%	1,603	23.9%	2,856	26.9%			
South	63	38.7%	425	37.7%	2,917	43.4%	3,536	33.3%			
West	13	8.0%	139	12.3%	621	9.2%	1,201	11.3%			
Index Year (n, %)											
2008	60	36.8%	450	39.9%	2,787	41.5%	4,861	45.8%			*

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Patient cohort	High Dose CS (HD) (N = 163)		Medium Dose CS (MD) (N = 1,127)		Low Dose CS (LD) (N = 6,717)		No-steroid Dose (NS) (N = 10,611)		p-value (HD vs. LD)	p-value (MD vs. LD)	p-value (NS vs. LD)
2009	26	16.0%	179	15.9%	1,045	15.6%	1,754	16.5%			
2010	32	19.6%	165	14.6%	939	14.0%	1,392	13.1%			
2011	20	12.3%	156	13.8%	874	13.0%	1,227	11.6%			
2012	16	9.8%	117	10.4%	711	10.6%	913	8.6%			
2013	9	5.5%	60	5.3%	361	5.4%	464	4.4%			
Physician Specialty (n, %)											
Rheumatologist	31	19.0%	231	20.5%	1,450	21.6%	2,075	19.6%			†
Cardiologist	1	0.6%	2	0.2%	28	0.4%	45	0.4%			
Pulmonologist	0	0.0%	7	0.6%	14	0.2%	21	0.2%		†	
Nephrologist	4	2.5%	24	2.1%	49	0.7%	90	0.8%	†	*	
Hematologist	1	0.6%	0	0.0%	4	0.1%	5	0.0%			
Neurologist	0	0.0%	6	0.5%	21	0.3%	25	0.2%			
Primary Care **	36	22.1%	205	18.2%	1,459	21.7%	2,048	19.3%		†	†
Other	90	55.2%	652	57.9%	3,692	55.0%	6,302	59.4%			*
Rheumatology Visit (n, %)	29	17.8%	220	19.5%	1,414	21.1%	1,756	16.5%			*
PCP Visit (n, %)	78	47.9%	537	47.6%	3,542	52.7%	4,634	43.7%		†	*
Hematology Visit (n, %)	0	0.0%	8	0.7%	31	0.5%	37	0.3%			
Nephrology Visit (n, %)	7	4.3%	36	3.2%	126	1.9%	199	1.9%	†	†	
Charlson Comorbidity Index (CCI) Score (n, %)											
0	72	44.2%	461	40.9%	2,966	44.2%	5,006	47.2%		†	†
1	54	33.1%	406	36.0%	2,526	37.6%	3,793	35.7%			
2	16	9.8%	136	12.1%	725	10.8%	1,006	9.5%			
3+	21	12.9%	124	11.0%	500	7.4%	806	7.6%			
Mean ± SD	1.0 ± 1.2		1.0 ± 1.2		0.9 ± 1.1		0.8 ± 1.1			*	†
Comorbidities of Interest: (n, %)											
Cardiovascular disease	30	18.4%	178	15.8%	910	13.5%	1,147	10.8%		†	*
Stroke	6	3.7%	40	3.5%	193	2.9%	283	2.7%			

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Patient cohort	High Dose CS (HD) (N = 163)		Medium Dose CS (MD) (N = 1,127)		Low Dose CS (LD) (N = 6,717)		No-steroid Dose (NS) (N = 10,611)		p-value (HD vs. LD)	p-value (MD vs. LD)	p-value (NS vs. LD)
Myocardial infarction	4	2.5%	16	1.4%	73	1.1%	101	1.0%			
Peripheral vascular disease	12	7.4%	85	7.5%	465	6.9%	663	6.2%			
Cerebrovascular disease	6	3.7%	37	3.3%	190	2.8%	290	2.7%			
Osteoporosis	5	3.1%	30	2.7%	233	3.5%	422	4.0%			
Infection	71	43.6%	467	41.4%	2,951	43.9%	3,829	36.1%			*
Diabetes	13	8.0%	90	8.0%	461	6.9%	809	7.6%			
Hypertension	39	23.9%	285	25.3%	1,659	24.7%	2,525	23.8%			
Renal disease	21	12.9%	115	10.2%	269	4.0%	470	4.4%	*	*	
Pre-index (6-month) Total Medical Costs											
Mean ± SD	$11,977 ± $47,389		$9,467 ± $27,462		$5,997 ± $22,541		$5,195 ± $21,958		†	*	†
Median	$2,248		$2,308		$1,944		$1,441			†	*
Pre-index (6-month) Total Pharmacy Costs											
Mean ± SD	$1,504 ± $3,499		$1,612 ± $3,376		$1,620 ± $2,984		$1,207 ± $2,865				*
Median	$373		$411		$630		$345		†	*	*
Concomitant Medications: (n, %)											
Corticosteroids	0	0.0%	0	0.0%	7	0.1%	4	0.0%			
NSAIDs	26	16.0%	286	25.4%	1853	27.6%	1965	18.5%	†		*
Anti-malarials	36	22.1%	277	24.6%	2245	33.4%	3338	31.5%	†	*	†
Immunosuppressants	9	5.5%	70	6.2%	251	3.7%	285	2.7%		†	*
Cyclophosphamide	0	0.0%	2	0.2%	1	0.0%	1	0.0%			
Mycophenolate mofetil	7	4.3%	36	3.2%	129	1.9%	159	1.5%	†	†	†

Abbreviations. HMO=Health Maintenance Organization, PPO=Preferred Provider Organization, POS=Point of Service, NSAIDs=Nonsteroidal Anti-Inflammatory Drugs

*=p<0.0001

†=p<0.05

** Primary care: primary care physician/family physician/general practitioner, internal medicine physician

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Table 2.

Healthcare resource utilization for the third year post-index

Patient cohort	High Dose CS (HD) (N = 163)		Medium Dose CS (MD) (N = 1,127)		Low Dose CS (LD) (N = 6,717)		No-steroid Dose (NS) (N = 10,611)		p-value (HD vs. LD)	p-value (MD vs. LD)	p-value (NS vs. LD)
PHARMACY SERVICES (NDC codes)											
Corticosteroids (n %)	105	64.4%	779	69.1%	2,764	41.1%	1,676	15.8%	*	*	*
Mean ± SD, Median	3.3 ± 4.1	2	3.8 ± 4.3	2	1.0 ± 2.0	0	0.3 ± 0.9	0	*	*	*
Immunosuppressants (n, %)	50	30.7%	374	33.2%	522	7.8%	434	4.1%	*	*	*
Mean ± SD, Median	1.6 ± 3.4	0	2.2 ± 4.1	0	0.4 ± 1.9	0	0.2 ± 1.5	0	*	*	*
Cyclophosphamide (n, %)	2	1.2%	5	0.4%	1	0.0%	3	0.0%	†	†	
Mean ± SD, Median	0.1 ± 1.6	0	0.0 ± 0.3	0	0.0 ± 0.2	0	0.0 ± 0.0	0	*	†	
Mycophenolate mofetil (n, %)	32	19.6%	220	19.5%	268	4.0%	234	2.2%	*	*	*
Mean ± SD, Median	0.9 ± 2.2	0	1.1 ± 2.8	0	0.2 ± 1.1	0	0.1 ± 0.9	0	*	*	*
Anti-malarials (n, %)	78	47.9%	642	57.0%	3,175	47.3%	3,950	37.2%		*	*
Mean ± SD, Median	3.0 ± 3.9	0	3.4 ± 4.1	2	2.7 ± 3.7	0	2.1 ± 3.5	0		*	*
Biologics (n, %)	0	0.0%	0	0.0%	0	0.0%	0	0.0%			
Mean ± SD, Median	0.0 ± 0.0	0	0.0 ± 0.0	0	0.0 ± 0.0	0	0.0 ± 0.0	0			
NSAIDs (n, %)	48	29.4%	322	28.6%	2,499	37.2%	2,695	25.4%	†	*	*

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Patient cohort	High Dose CS (HD) (N = 163)		Medium Dose CS (MD) (N = 1,127)		Low Dose CS (LD) (N = 6,717)		No-steroid Dose (NS) (N = 10,611)		p-value (HD vs. LD)	p-value (MD vs. LD)	p-value (NS vs. LD)
Mean ± SD, Median	0.8 ± 1.8	0	1.2 ± 2.7	0	1.4 ± 2.7	0	0.9 ± 2.2	0	†	†	*
All other pharmacy (n, %)	158	96.9%	1,090	96.7%	6,400	95.3%	8,886	83.7%		†	*
Mean ± SD, Median	42.1 ± 39.9	28	40.7 ± 36.2	30	34.4 ± 32.8	25	22.5 ± 26.5	14	†	*	*
EMERGENCY ROOM SERVICES (n, %)	64	39.3%	378	33.5%	1,996	29.7%	2,381	22.4%	†	†	*
Mean ± SD, Median	1.0 ± 2.1	0	0.8 ± 2.4	0	0.6 ± 1.9	0	0.4 ± 1.7	0	†	†	*
OUTPATIENT SERVICES (n, %)											
Physician office visits (n, %)	160	98.2%	1,108	98.3%	6,557	97.6%	10,140	95.6%			*
Mean ± SD, Median	22.8 ± 30.8	13	18.6 ± 20.9	13	15.7 ± 16.4	11	12.8 ± 17.2	8	*	*	*
Rheumatology (n, %)	52	31.9%	445	39.5%	2,240	33.3%	2,651	25.0%		*	*
Mean ± SD, Median	1.0 ± 2.1	0	1.4 ± 2.4	0	1.0 ± 1.8	0	0.6 ± 1.4	0		*	*
All others (n, %)	159	97.5%	1,096	97.2%	6,517	97.0%	10,089	95.1%			*
Mean ± SD, Median	21.8 ± 30.5	12	17.2 ± 20.8	11	14.7 ± 16.3	10	12.2 ± 17.1	8	*	*	*
Laboratory and pathology (n, %)	157	96.3%	1,079	95.7%	6,259	93.2%	9,491	89.4%		†	*
Mean ± SD, Median	45.2 ± 48.4	34	39.1 ± 40.6	28	25.4 ± 27.4	19	20.3 ± 26.2	14	*	*	*

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Patient cohort	High Dose CS (HD) (N = 163)		Medium Dose CS (MD) (N = 1,127)		Low Dose CS (LD) (N = 6,717)		No-steroid Dose (NS) (N = 10,611)		p-value (HD vs. LD)	p-value (MD vs. LD)	p-value (NS vs. LD)
Radiology examinations (n, %)	135	82.8%	872	77.4%	5,243	78.1%	7,678	72.4%			*
Mean ± SD, Median	5.8 ± 10.1	3	4.3 ± 7.0	2	4.0 ± 5.5	2	3.2 ± 5.4	2	*		*
Surgical services (n, %)	98	60.1%	622	55.2%	3,722	55.4%	4,851	45.7%			*
Mean ± SD, Median	2.6 ± 4.4	1	2.0 ± 3.6	1	1.9 ± 3.3	1	1.4 ± 2.8	0	†		*
Ancillary services (n, %)	157	96.3%	1,075	95.4%	6,251	93.1%	9,584	90.3%		†	*
Mean ± SD, Median	33.0 ± 62.8	14	20.7 ± 31.9	11	14.6 ± 20.9	8	11.8 ± 23.9	6	*	*	*
Dialysis (n, %)	8	4.9%	13	1.2%	43	0.6%	57	0.5%	*		
Mean ± SD, Median	1.5 ± 11.8	0	1.4 ± 15.9	0	0.3 ± 6.4	0	0.4 ± 8.8	0	†	*	
HCPCS SERVICES (J codes)											
Corticosteroids (n, %)	42	25.8%	347	30.8%	2,217	33.0%	2,110	19.9%			*
Mean ± SD, Median	0.7 ± 2.0	0	0.8 ± 2.0	0	0.8 ± 1.7	0	0.4 ± 1.4	0			*
Immunosuppressants (n, %)	6	3.7%	32	2.8%	32	0.5%	22	0.2%	†	*	†
Mean ± SD, Median	0.1 ± 0.7	0	0.1 ± 1.1	0	0.0 ± 0.2	0	0.0 ± 0.4	0	*	*	
Cyclophosphamide (n, %)	4	2.5%	20	1.8%	19	0.3%	13	0.1%	†	*	†
Mean ± SD, Median	0.1 ± 0.4	0	0.1 ± 0.6	0	0.0 ± 0.2	0	0.0 + 0.2	0	†	*	
Mycophenolate mofetil (n, %)	1	0.6%	6	0.5%	10	0.1%	5	0.0%		†	†

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Patient cohort	High Dose CS (HD) (N = 163)		Medium Dose CS (MD) (N = 1,127)		Low Dose CS (LD) (N = 6,717)		No-steroid Dose (NS) (N = 10,611)		p-value (HD vs. LD)	p-value (MD vs. LD)	p-value (NS vs. LD)
Mean ± SD, Median	0.0 ± 0.1	0	0.0 ± 0.4	0	0.0 ± 0.1	0	0.0 ± 0.1	0		†	
Anti-malarials (n, %)	0	0.0%	0	0.0%	0	0.0%	1	0.0%			
Mean ± SD, Median	0.0 ± 0.0	0	0.0 ± 0.0	0	0.0 ± 0.0	0	0.0 ± 0.0	0			
Biologics (n, %)	0	0.0%	0	0.0%	0	0.0%	0	0.0%			
Mean ± SD, Median	0.0 ± 0.0	0	0.0 ± 0.0	0	0.0 ± 0.0	0	0.0 ± 0.0	0			
All other HCPCS (n, %)	77	47.2%	502	44.5%	2,637	39.3%	2,989	28.2%	†	†	*
Mean ± SD, Median	4.9 ± 11.6	0	5.5 ± 21.4	0	2.9 ± 12.6	0	2.2 ± 15.1	0		*	†
NUMBER OF INPATIENT HOSPITALIZATIONS											
One or more hospitalizations (n, %)	35	21.5%	198	17.6%	828	12.3%	1,007	9.5%	†	*	*
Mean ± SD, Median	0.7 ± 2.4	0	0.4 ± 1.2	0	0.2 ± 0.7	0	0.1 ± 0.7	0.7 0	*	*	*
Total Days (Mean + SD, Median)	6.1 + 21.6	0	2.2 + 10.0	0	1.2 + 9.1	0	0.9 + 6.5	0	*	†	†

Abbreviations. HCPCS=Healthcare Common Procedure Coding System

*=p<0.0001

†=p<0.05

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Table 3:

Generalized linear model of total all-cause healthcare costs during the third year post-index

Variable	Cost Ratio (95% CI)	95% Confidence Limits		
		Lower Limit	Upper Limit	p-value
Steroid Exposure Group (Reference group: low)				
Non-Steroid Use	0.72 (0.70–0.75)	0.697	0.754	*
Medium	1.71	1.571	1.850	*
High	2.80	2.290	3.420	*
Age (continuous)	1.01	1.004	1.008	*
Gender (Reference group: Male)	1.01	0.951	1.080	
Charlson comorbidity index	1.19	1.165	1.214	*
Cardiovascular disease	1.28	1.209	1.363	*
Renal disease	1.66	1.507	1.824	*
Log (Total medical costs)	1.06	1.054	1.065	*
NSAIDs	1.11	1.060	1.160	*
Anti-malarials	0.84	0.802	0.870	*

*=p<0.0001

†=p<0.05