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Real-world treatment utilization and economic implications of lupus nephritis disease activity in the United States

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Plain language summary

A common problem with lupus is damage in the kidneys (lupus nephritis). This damage can lead to the kidneys not working correctly (kidney failure). There are times of active disease in the kidneys and times when the disease is quiet (low disease activity). This study reviews the costs and drugs used in active disease, low disease activity, or kidney failure. The study found that drug costs are the highest during active disease or kidney failure.

Implications for managed care pharmacy

This is the first study to describe the economic implications of high and low disease activity and end-stage renal disease (ESRD) in lupus nephritis (LN). Monthly medical costs were doubled for high disease activity periods and were 7 times higher for ESRD vs low disease activity periods. Because active LN is evident in approximately two-thirds of patients, treatments that can achieve low disease activity remain a significant unmet need in the treatment of LN.

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ABSTRACT

BACKGROUND: Lupus nephritis (LN) is a common and severe complication of systemic lupus erythematosus (SLE), with approximately 40% of patients with SLE developing LN. Even with treatment, 10%-30% of patients will progress to end-stage renal disease (ESRD). Although many studies have assessed the clinical value of low disease activity in LN, the economic implications are less defined.

OBJECTIVE: To evaluate treatment utilization and health care costs associated with active disease, low disease activity, and ESRD in patients with LN.

METHODS: A retrospective analysis of Optum pharmacy and medical claims data from 2015 to 2019 was performed and included patients with a diagnosis of SLE (*International Classification of Diseases, Ninth Revision* or *Tenth Revision* codes 710.0 or M32, respectively) and additional prespecified criteria for LN. Total health care payer costs for medical and pharmacy services and treatment utilization for commonly prescribed medications were determined for periods of low disease activity, active disease, or ESRD.

RESULTS: A total of 21,251 patients (mean age 60.3 years; 87% female; 55% White patients and 18% Black patients) with a mean follow-up period of 30.6 months were included; the majority of patients had active disease (67.3%), followed by low disease activity (51.3%), and ESRD (10.5%). Glucocorticoids were used 2 times more often and mycophenolate mofetil was used 4 times more often in patients with active disease vs low disease activity. Glucocorticoids, mycophenolate mofetil, and tacrolimus were more commonly used in patients with ESRD vs those with low disease activity. Mean

medical costs were $4,777 per month in active disease and $18,084 per month in ESRD vs $2,523 per month in low disease activity.

CONCLUSIONS: Treatment burden and costs are high for patients with active disease and ESRD in LN. Treatments that allow patients to achieve and maintain low disease activity may help improve patient outcomes and reduce medication use and overall health care costs.

Lupus nephritis (LN) is a common and severe complication of systemic lupus erythematosus (SLE) that can cause irreversible nephron loss, thus reducing the life span of the kidneys, and may ultimately lead to end-stage renal disease (ESRD).[1] Patients diagnosed with LN have 3 times the risk of mortality compared with patients with SLE and no renal involvement.[2] Approximately 40% of patients with SLE will develop LN,[3] and 35% will present with LN at initial diagnosis of SLE.[4] LN features alternating periods of active disease (ie, flares or relapses) and low disease activity. Potent initial therapy with moderate- to high-dose glucocorticoids and mycophenolate mofetil (MMF) or cyclophosphamide is used during active disease with the goal of suppressing the immune-mediated inflammation, whereas subsequent therapy using lower-dose MMF or azathioprine is aimed at consolidating the initial response, maintaining the renal response, and preventing flares.[5]

However, even with treatment, 10%-30% of patients with LN will progress to ESRD within 15 years of diagnosis and will require dialysis or kidney transplant.[6] For this reason, one of the main goals of treatment is to preserve long-term kidney function by achieving complete response,[7,8] which includes a reduction in proteinuria (urine protein creatinine ratio <0.5 to 0.7 gm per 24 hours) and improvement or stabilization of estimated glomerular filtration rate.[7] Decreases in proteinuria within 6 to 12 months of initiating treatment are associated with better long-term outcomes, such as decreased risk of mortality and ESRD.[9-15]

Although the clinical value of achieving low disease activity has been well documented,[9-15] the economic implications are less well defined, and only a few studies have assessed real-world treatment of LN. Previous studies had small sample sizes (range: 900-2,300 patients)[16-19] or analyzed outcomes in specific populations, such as patients enrolled in Medicaid.[18] A recent prospective study in patients with SLE determined that spending more than 50% of time in low disease activity was associated with a 47% reduction in annual direct medical costs.[20] Although that study evaluated the impact of low disease activity on costs, no such studies have been conducted in patients with LN specifically.

Thus, the purpose of this study was to evaluate treatment utilization and health care payer costs associated with active disease, low disease activity, and ESRD in patients with LN.

Methods

STUDY DESIGN AND DATA SOURCE

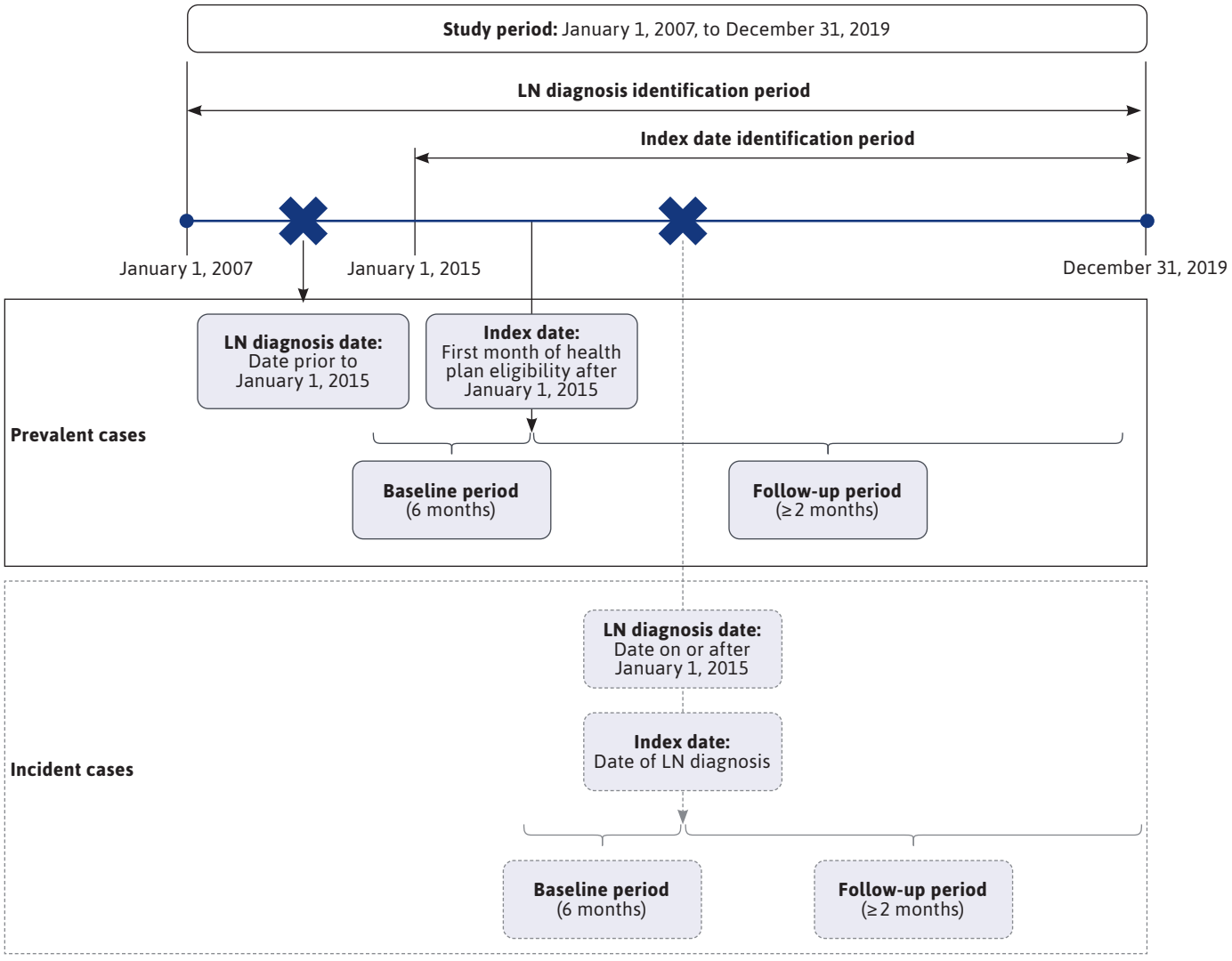
This descriptive study was a retrospective, observational analysis using Optum pharmacy and medical claims data dated between January 1, 2007, and December 31, 2019 (Figure 1). The Optum database includes US health care plan data on more than 111 million patients with commercial or Medicare with Part D coverage and includes demographic information, *International Classification of Diseases, Ninth Revision* and *Tenth Revision* (ICD-9; ICD-10) codes, Current Procedural Terminology codes, Healthcare Common Procedure Coding System codes for inpatient and outpatient diagnoses and procedures, and prescription information such as National Drug Code. Primary data were not collected in this study; all data were ascertained from the previously anonymized Optum pharmacy and medical claims data. Therefore, institutional review board approval and informed consent were not required. Patients enrolled in Medicaid were not captured in this database.

STUDY POPULATION

Patients with evidence of any diagnosis of SLE (ICD-9: 710.0 or ICD-10: M32) with 1 or more inpatient admission or 2 or more outpatient admissions 30 days apart between January 1, 2015, and December 31, 2019, were included in the study. Because of the nonspecificity of ICD-9 codes in identifying LN (ICD-9 codes were used prior to October 1, 2015), and because LN is often undercoded in claims data, inclusion criteria from previous studies that evaluated LN in administrative claims data were evaluated by our clinical experts and adopted for patient identification.[16,21] Patients had to meet 1 or more of the following criteria for inclusion in the analysis: 2 or more outpatient or 1 or more inpatient events associated with a diagnosis of glomerular disease in SLE (ICD-10: M32.14), a diagnosis of SLE with at least 1 nephrology visit, a diagnosis of an acute or chronic renal condition, evidence of ESRD (eg, diagnosis code, dialysis, use of phosphate binder or renal transplant) after SLE diagnosis, or use of medication for treatment of LN (see Supplementary Table 1, available in online article, for full criteria and codes).

Patients were categorized as prevalent or incident, in which incident cases were defined as having 6 months of eligibility without evidence of LN before the first LN

FIGURE 1 Study Design



LN = lupus nephritis.

diagnosis, which occurred after January 1, 2015 (Figure 1). Prevalent cases were defined as having evidence of LN prior to January 1, 2015. The index date for prevalent cases was the first month of eligibility during the study period, whereas the index date for incident cases was the date the patient met the LN case definition during the study period. The follow-up (post-index) period included the period following the index date, which was used to assess costs and treatment utilization. Adult patients (≥18 years) with at least 2 months of continuous enrollment were followed until death, loss to follow-up, or the end of the study period.

FOLLOW-UP CLASSIFICATIONS AND ENDPOINT DEFINITIONS

Patient follow-up time was classified as periods of low disease activity, active disease, or ESRD; thus, patients were not mutually exclusive to each cohort. Low disease activity was evaluated across each patient's follow-up period and was defined as at least 6 consecutive months of glucocorticoid dose less than or equal to 5 mg per day, MMF dose less than or equal to 2 gm per day, and no use of cyclophosphamide. For the glucocorticoid dose, the prednisone equivalent dose was calculated and included oral and intravenous

administration. Time without evidence of low disease activity or ESRD was classified as active disease. Patients were defined as being in ESRD if there was evidence of at least 1 ESRD diagnosis code, use of dialysis, treatment with phosphate binders, or kidney transplant.

The primary endpoints included total health care payer costs for all-cause medical and pharmacy services during periods of active disease, low disease activity, and ESRD and treatment utilization of commonly prescribed medications for LN. Treatment utilization was based on claims for prescription drugs dispensed (retail and mail order) and included all glucocorticoids (intravenous and oral), MMF, azathioprine, cyclophosphamide, calcineurin inhibitors (cyclosporine and tacrolimus), rituximab, and belimumab. Frequency and time to mortality were secondary endpoints.

Health care payer costs were defined as the total amount paid for all-cause medical and pharmacy services, including costs related to LN and conditions other than LN. Costs were categorized as pharmacy, inpatient visits, emergency department visits, physician office visits, and other outpatient services (eg, laboratory services, outpatient treatment, diagnostic tests). LN-related medications billed through the medical benefit were classified as pharmacy costs and included all medications included in the prescription claims analysis. Given the differential follow-up time across patients, costs were presented as monthly costs per patient and adjusted to 2020 US dollars.

Additionally, the frequency of use of long-term glucocorticoids (LTGs) was evaluated in a subset of patients who were followed for at least 12 consecutive months. LTG use was defined as evidence of glucocorticoid use for at least 6 months, with a medication possession ratio of 0.80 or more to account for potential nonadherence (1.0 represents complete adherence). Medication possession ratio was defined as the number of days of therapy during evidence of LTG divided by the maximum number of possible days between the first and last qualifying glucocorticoid prescription. The assessment of LTG was not restricted to specific disease activity time frames, as patients could have evidence of LTG in multiple disease states (ie, active disease, low disease activity, or ESRD).

Additionally, the Quan-Charlson Comorbidity Index (CCI) and data on selected comorbidities, including diabetes (with and without end-organ damage), myocardial infarction, congestive heart failure, chronic pulmonary disease, cerebrovascular disease, all tumors (including leukemia and lymphoma), infections (influenza, acute bronchitis, pneumonia, bacterial, or urinary tract infection), hypertension, gastrointestinal symptoms (bleeding; diarrhea; cramping; or bloody, black, or tarry stool), psychiatric issues (cognitive impairment, memory loss, dementia, or insomnia), skin conditions (ie, rashes, purpura), edema, and osteoporosis were collected, as they are associated with LTG use.

STATISTICAL METHODOLOGY

Baseline and demographic patient characteristics were analyzed descriptively using percentages, means, and SDs in patients by active disease, low disease activity, and ESRD, including all patients who met the criteria of the specified period at least once during the study. Comorbidities were assessed using the Quan-CCI score. Endpoint results are presented descriptively for periods of active disease, low disease activity, and ESRD. P values were not calculated for comparisons. Differences between patients with commercial and Medicare with Part D coverage are highlighted.

Results

There were 101,972 patients with evidence of SLE from January 2007 to October 2019. Of these patients, 38,679 (37.9%) had evidence of LN, with 28,891 who were present in the database as of or after January 1, 2015 (see Supplementary Figure 1). After applying eligibility criteria for the study, the final sample size was 21,251, retaining 73.6% of the eligible sample (see Supplementary Table 1 for the classification of patients meeting each criterion for a diagnosis of LN). A total of 53.6% (n=11,380) of the eligible sample was defined as incident cases and 46.5% (n=9,871) was defined as prevalent cases. Mean follow-up time of the sample was 30.6 months.

BASELINE PATIENT CHARACTERISTICS

The majority of patients were female (86.9%), White (55.2%), and from the South (47.1%) (Table 1). Low disease activity was evident in 51.3% of patients, with a mean duration of 27.5 months. There was evidence of active disease in 67.3% of patients, with a mean duration of 20.5 months. ESRD was evident in 10.5% of patients; mean time to ESRD was 18 months from study index.

Patients having evidence of low disease activity were older (mean age: 62.4 years) when compared with patients with active disease (mean age: 59.4 years) or ESRD (mean age: 58.0 years). The older age across all cohorts was driven by a high Medicare population, with 61.9% of the sample being enrolled in Medicare (mean age: 67.9 years) compared with 38.1% enrolled in commercial insurance (mean age: 47.8 years). Although the distributions of sex and race were similar in patients with low disease activity and active disease, ESRD had a lower proportion of females (ESRD: 80.6%; active disease: 87.7%; low disease activity: 87.7%) and White patients (ESRD: 49.6%; active disease: 55.2%; low disease activity: 57.1%).

TABLE 1 Baseline Patient Characteristics

Patient characteristic	Overall sample N = 21,251		Low disease activity n = 10,911		Active disease n = 14,310		End-stage renal disease n = 2,240	
Age, mean ± SD	60.3 ± 15.7		62.4 ± 15.1		59.4 ± 15.7		58.0 ± 15.7	
Quan-CCI, mean ± SD	2.35 ± 2.01		2.20 ± 1.90		2.30 ± 2.00		2.90 ± 2.30	
Sex								
Female	18,470	(86.9)	9,570	(87.7)	12,555	(87.7)	1,805	(80.6)
Male	2,774	(13.1)	1,337	(12.3)	1,752	(12.2)	434	(19.4)
Unknown	7	(0)	4	(0)	3	(0)	1	(0)
Race and ethnicity								
White	11,733	(55.2)	6,234	(57.1)	7,893	(55.2)	1,110	(49.6)
Black	3,734	(17.6)	1,808	(16.6)	2,550	(17.8)	550	(24.6)
Hispanic	3,089	(14.5)	1,604	(14.7)	2,078	(14.5)	333	(14.9)
Asian	666	(3.1)	324	(3.0)	445	(3.1)	82	(3.7)
Unknown	2,029	(9.6)	941	(8.6)	1,344	(9.4)	165	(7.4)
Comorbidities								
Hypertension	12,928	(60.8)	6,597	(60.5)	8,567	(59.9)	1,521	(67.9)
Gastrointestinal symptoms	7,024	(33.1)	2,471	(22.7)	3,708	(25.9)	589	(26.3)
Any infection	6,491	(30.5)	3,022	(27.7)	4,506	(31.5)	738	(33.0)
Diabetes[a]	6,231	(29.3)	3,233	(29.6)	4,029	(28.2)	804	(35.9)
Chronic pulmonary disease	2,614	(12.3)	1,408	(12.9)	1,966	(13.7)	344	(15.4)
Psychiatric events	2,611	(12.3)	1,162	(10.7)	1,566	(10.9)	191	(8.5)
Edema	2,609	(12.3)	1,178	(10.8)	1,787	(12.5)	361	(16.1)
Congestive heart failure	2,547	(12.0)	1,165	(10.7)	1,660	(11.6)	409	(18.3)
Osteoporosis	2,470	(11.6)	1,184	(10.9)	1,702	(11.9)	211	(9.4)
Cerebrovascular disease	1,809	(8.5)	910	(8.3)	1,133	(7.9)	233	(10.4)
Skin conditions	1,526	(7.2)	685	(6.3)	1,054	(7.4)	112	(5.0)
Any tumors[b]	1,413	(6.7)	665	(6.1)	987	(6.9)	151	(6.7)
Myocardial infarction	879	(4.1)	395	(3.6)	566	(4.0)	108	(4.8)
Region								
Northeast	1,938	(9.1)	990	(9.1)	1,255	(8.8)	193	(8.6)
Midwest	3,719	(17.5)	1,814	(16.6)	2,529	(17.7)	405	(18.1)
South	10,016	(47.1)	4,885	(44.8)	6,925	(48.4)	1,203	(53.7)
West	5,542	(26.1)	3,205	(29.4)	3,576	(25.0)	433	(19.3)
Other/unknown	36	(0.2)	17	(0.2)	25	(0.2)	6	(0.3)
Payer type								
Commercial	8,101	(38.1)	3,645	(33.4)	5,642	(39.4)	930	(41.5)
Medicare	13,150	(61.9)	7,266	(66.6)	8,668	(60.6)	1,310	(58.5)

Values are the number (percentage), unless otherwise indicated. Baseline characteristics were assessed during the 6-month pre-index period, including the index date.

[a]*With and without organ damage.*

[b]*Including leukemia and lymphoma.*

Quan-CCI = Quan-Charlson Comordity Index.

TABLE 2 Treatment Utilization for Active Disease, Low Disease, and End-Stage Renal Disease

Treatment	Overall sample N = 21,251		Low disease activity n = 10,911		Active disease n = 14,310		End-stage renal disease n = 2,240	
Glucocorticoid	16,043	(75.5)	4,741	(43.5)	12,789	(89.4)	1,563	(69.8)
Antihypertensive	11,621	(54.7)	5,721	(52.4)	7,444	(52.0)	1,180	(52.7)
Statin	8,696	(40.9)	4,462	(40.9)	5,393	(37.7)	934	(41.7)
Mycophenolate mofetil	2,538	(11.9)	415	(3.8)	2,007	(14.0)	430	(19.2)
Azathioprine	1,697	(8.0)	521	(4.8)	1,289	(9.0)	148	(6.6)
Rituximab	979	(4.6)	214	(2.0)	790	(5.5)	66	(3.0)
Belimumab	675	(3.2)	180	(1.7)	570	(4.0)	33	(1.5)
Tacrolimus	478	(2.3)	37	(0.3)	143	(1.0)	333	(14.9)
Cyclophosphamide[a]	427	(2.0)		–	337	(2.4)	67	(3.0)
Cyclosporine	165	(0.8)	33	(0.3)	83	(0.6)	61	(2.7)

Values are the number (percentage), unless otherwise indicated.

[a]*No use of cyclophosphamide was a criterion for low disease activity.*

Baseline comorbidities were assessed in the 6-month pre-index period, including the index date, by the Quan-CCI and by evaluating specific comorbidities associated with LN. The CCI was similar in patients with active disease (2.3) and low disease (2.2), whereas ESRD patients had the highest CCI (2.9); 70.2% of ESRD patients had a CCI greater than or equal to 2 compared with roughly 55% of patients in the active and low disease cohorts. When evaluating the distribution of comorbidities associated with LN, patients having low disease activity did not have the highest risk in any comorbidity category. Patients with low disease activity tended to have a similar or slightly lower risk of comorbidities when compared with active disease patients, whereas patients with ESRD had the highest risk of hypertension, diabetes, edema, congestive heart failure, and cerebrovascular disease.

TREATMENT UTILIZATION

As seen in Table 2, although glucocorticoids were the most frequently used medication across all cohorts, use of glucocorticoids was observed in almost twice as many patients with active disease (89.4%) than those with low disease activity (43.5%). With the exceptions of antihypertensives and statins, low disease patients tended to have the lowest rate of LN treatments. Antihypertensive (52.0%-52.7%) and statin (37.7%-41.7%) use was similar across the cohorts. The rate of MMF use was approximately 4 times higher in active disease patients (14.0%) and 5 times higher in ESRD patients (19.2%) compared with low disease activity patients (3.8%). When comparing MMF rates by insurance types, Medicare patients were less likely to have evidence of MMF use (6.3%) compared with commercially insured patients (21.0%). Tacrolimus was used in 14.9% of ESRD patients and less than or equal to 1.0% of patients with active disease or low disease activity.

LTG use (≥6 months) was not assessed within specific disease time frames (ie, the cohorts were not mutually exclusive). Accordingly, 17.2% of patients with active disease had evidence of LTG use compared with 10.7% of patients with low disease activity and 5.5% of ESRD patients.

HEALTH CARE COSTS

All-cause medical costs were almost twice as high during active disease periods, with a mean of $4,777 per month compared with $2,523 per month for periods of low disease activity (Table 3). Costs associated with inpatient, emergency department, physician office, and other outpatient visits were lower for patients with low disease activity vs active disease, with the greatest difference seen between inpatient costs ($1,406 vs $2,896). Similarly, pharmacy costs were lower for periods of low disease activity ($1,061) compared with high disease activity ($1,835). After factoring in pharmacy costs, monthly total health care payer costs for active disease periods were $3,028 higher per month compared with periods of low disease activity.

The mean monthly all-cause medical cost for patients with ESRD was $18,084 (Table 3). The main medical cost drivers were inpatient visits ($13,756) and other outpatient visits ($3,013). Monthly pharmacy costs were $3,760, bringing mean monthly total payer costs for all health care to $21,844 for patients with ESRD.

TABLE 3 Health Care Costs for Active Disease, Low Disease Activity, and End-Stage Renal Disease

Monthly cost, mean	Low disease activity n=10,911	Active disease n=14,310	End-stage renal disease n=2,240
Medical	$2,523	$4,777	$18,084
Inpatient	$1,406	$2,896	$13,756
Emergency department	$281	$657	$663
Physician office	$304	$457	$655
Other outpatient	$532	$768	$3,013
Pharmacy	$1,061	$1,835	$3,760
Total	$3,584	$6,612	$21,844
Medicare	n=7,266	n=8,668	n=1,310
Medical	$2,889	$5,124	$20,457
Pharmacy	$1,095	$1,781	$4,793
Total	$3,984	$6,905	$25,250
Commercial	n=3,645	n=5,642	n=930
Medical	$1,794	$4,243	$14,741
Pharmacy	$993	$1,920	$2,305
Total	$2,787	$6,163	$17,047

When costs were stratified by type of insurance, the overall mean monthly all-cause health care cost was slightly higher for Medicare patients ($6,305) compared with commercial patients ($5,057). Regardless of insurance type, lower costs were seen in low disease activity compared with active disease and ESRD (Table 3). The difference in total monthly costs with active vs low disease activity for Medicare patients was $2,921 and for commercial patients was $3,376. Total monthly all-cause health care costs for Medicare patients in ESRD were $25,250; the total costs for commercial patients were $17,047.

DEATH

Overall, 11.6% of patients (n=2,462) died over the follow-up period. Mean time to death was 23.7 months after study index. The rate of death in patients with ESRD was 24.3% compared with 11.0% in active and 10.0% in low disease patients.

Discussion

This is the first and largest study, to our knowledge, that captures real-world treatment utilization and economic implications associated with low disease activity, active disease, and ESRD in patients with LN in a US population. Previous studies in LN have described treatment utilization and associated costs of care but did not specifically assess differences between disease activity levels. Results from the current study indicated that patients with active disease have higher health care costs than patients with low disease activity ($6,612 vs $3,584) and supports that these patients have high treatment burden, including high glucocorticoid use, as they are initiating therapy for LN or treating a flare. Given that 67.3% of patients had evidence of active disease, treatments that help patients achieve and maintain low disease activity remain a significant unmet need within the treatment landscape for LN.

Relative to low disease activity, the economic burden for patients with active disease and ESRD was substantial. Monthly all-cause medical costs for periods of active disease were twice as high and costs for ESRD were 7 times as high when compared with periods of low disease activity. The death rate associated with ESRD (24%) was also more than twice as high compared with low disease activity (10%) and active disease (11%). As previous studies have correlated disease status in LN with long-term renal survival, our results indicate that early intervention and rapid management of active disease periods to help achieve lower disease activity would reduce the economic burden and reduce the risk of mortality associated with the development of ESRD.

In the current study, 51.3% of patients had evidence of low disease activity during follow-up. Although low disease activity was defined in this study by at least 6 consecutive months of glucocorticoid dose less than or equal to 5 mg per day, MMF dose less than or equal to 2 gm per day, and no use of cyclophosphamide, this percentage aligns with previous research, which reported that 40.9%-59.1% of patients had low disease activity at 24 months post-LN diagnosis, as assessed by clinical response based on various laboratory measures of renal function and activity.[11] Additionally, 10% of patients in our study had evidence of ESRD, which aligns with previous estimated ranges of 10%-30%.[6]

This study also provided updated information on treatment utilization of medications used in LN and showed a higher treatment burden for patients with active disease and ESRD. Regardless of disease status, glucocorticoids were the most frequently used medication, being more heavily used in periods of active disease (89.4%) and ESRD (69.8%) compared with low disease activity (43.5%). The frequent use of glucocorticoids in active disease is consistent with guidelines for treating kidney flares in LN[7]; glucocorticoids are also used as maintenance therapy in patients who are candidates or have received kidney transplantation.[22] Long-term use of glucocorticoids is associated with many adverse effects, including some that

can be quite costly, such as serious infections, osteoporotic fractures, diabetes mellitus, psychiatric events, and premature mortality.[3,23] As such, there has been a recent focus to reduce glucocorticoid dose and rapidly taper after 6 months in patients with LN.[7] Evidence of LTG use was highest in patients with active disease.

MMF use was approximately 4 times higher in active disease patients and 5 times higher in ESRD patients compared with low disease activity, and tacrolimus use was substantially higher (~15%) in ESRD patients compared with active disease or low disease activity patients (≤1%); this may be related to the use of tacrolimus as maintenance therapy for kidney transplantation.[22] The overall rate of MMF use was lower than expected (11.9%) in our study. In the study by Bartels-Peculis et al, 30% of patients had evidence of MMF use; however, this population was substantially younger, with a mean age of 47 years, compared with patients in the current study, who had a mean age of 60 years.[16] An earlier study using data from a national managed care organization with 907 LN patients showed similar results to Bartels-Peculis et al, with 50% of the overall cohort aged between 18 and 44 years and 21% using MMF.[17] In a comparison of MMF rates by insurance type in the current study, commercially insured patients were twice as likely to have evidence of MMF use (21.0%) compared with patients with Medicare with Part D coverage (9.4%). It is possible that patients may have received medications such as MMF through prescription assistance programs or coupon discount programs, such as GoodRx or NeedyMeds, Inc., that would not be captured in the dataset used for this study.

The rates of use of antihypertensives and statins were similar across cohorts, with about 50% and 40% of all patients using each, respectively. The most recent American College of Rheumatology guidelines for LN recommend antihypertensives for all LN patients with proteinuria greater than or equal to 0.5 gm per 24 hours (or equivalent by protein/creatinine ratios on spot urine samples) and statin therapy for patients with low-density lipoprotein cholesterol >100 mg/dL.[5] These rates of antihypertensive and statin use are expected given the comorbidity rates in this study sample for hypertension (60.8%) and cardiovascular disease (12.3% for chronic pulmonary disease, 8.5% for congestive heart failure, 4.1% for myocardial infarction).

One advantage of the current study is that it used a much shorter minimum follow-up period than previous studies on treatment utilization and costs.[16-19] The current study required at least 2 months of follow-up after the index date; however, most previous studies have imposed a 12-month follow-up minimum following LN index date, which substantially reduces sample size and potentially the generalizability of results.[16-19] Patients with LN may die within the year after being identified for study inclusion or could transition to Medicare fee-for-service; therefore, exclusion of these patients may significantly underestimate the true costs incurred by payers. For example, the recent Bartels-Peculis study that imposed such restrictions indicated that total mean all-cause costs were $3,789 per month ($45,469 per year),[16] whereas the current study showed total mean all-cause costs of $5,829 per month. Mean follow-up for the current study was approximately 2.5 years; therefore, allowing a 2-month minimum follow-up did not shorten follow-up. The use of a variable follow-up time maximizes the opportunity to capture periods of active disease and low disease activity and correspondingly assesses how patients are treated during these periods. The inclusion criteria for this analysis were broad and could include patients with at least 1 diagnosis of a renal condition based on ICD-9 codes (Supplementary Table 1) instead of at least 2, as seen in a previous study.[21] A sensitivity analysis was performed excluding patients with only 1 diagnosis code, which showed that excluding those patients had minimal impact on the costs and the observed trends remained the same.

LIMITATIONS

Research conducted with claims data has inherent limitations, including possible coding errors, lack of information on treatments obtained outside of an insurance setting, lack of detailed clinical information (eg, disease severity) and treatment adherence, and reasons underlying choice and provision of treatment. As noted, it is possible that patients may have received medications through other means that may not have been captured in the claims data; therefore, the results of the current study may be an underestimation of medication use. As disease activity periods were defined by observed treatment utilization and not clinical or serological parameters, decreased use of steroids, MMF, and cyclophosphamide in the low disease arm is expected. Additionally, missing medication claims may have caused patients to be misclassified with low disease activity, which means the cost differences observed in this study may be a conservative estimate of the economic implications of low disease activity. However, disease state estimates, as defined by treatment utilization in the current study, do align with clinically defined disease states.[11] Additionally, some treatments used for LN are also used for SLE and in kidney transplantation; thus, it is difficult to extricate which treatments were used specifically for LN. Our study included a large Medicare insurance population, and the design of the study required these patients to have Medicare Part D for prescription coverage. Results may not be generalizable to

the overall Medicare population. Many patients with ESRD have Medicare Part B coverage with or without Part D; as such, the study may not be reflective of Medicare patients without Part D coverage.

The study population consisted of commercially insured and Medicare-insured patients in the Optum database, and results may not be generalizable to the overall LN population. Future studies should be conducted in a Medicaid population for comparison. Almost 40% of patients initially identified in the database with SLE had evidence of LN, consistent with earlier reports.[24] Rigorous inclusion criteria further reduced the studied population to 21,251 patients. Though LN affects primarily Black and Hispanic patients,[24] the current sample was predominantly White patients (55.2%), with only 17.6% Black and 14.5% Hispanic patients. The mean age of the sample was 60 years, higher than other studies. Additionally, treatment utilization may differ according to disease duration, provider type, patient preference, and other characteristics that were not measured in the current study. The current study only assessed costs incurred to payers and did not assess patient costs for medications and services or indirect costs of LN (eg, work loss and productivity). Future research should seek to quantify the full cost of illness related to LN.

Conclusions

In summary, treatment burden and costs associated with active disease and ESRD in LN are high in comparison with low disease activity. Glucocorticoid and MMF use are more frequent in patients with active disease and ESRD, tacrolimus use is much more common in ESRD patients, and LTG use is higher in patients with active disease. Additionally, the mortality rate is twice as high for ESRD patients. Mean monthly all-cause medical costs were much lower for periods of low disease activity, as costs were twice as high for periods of active disease and 7 times as costly for ESRD. Given the high rates of patients with active disease and poor outcomes associated with active disease, there remains significant unmet need in the treatment landscape for LN. The current study suggests that achieving low disease activity in LN patients is associated with reduced economic burden to health care payers; as such, treatments that allow patients to achieve and maintain low disease activity may help improve patient outcomes and reduce overall health care costs.

DISCLOSURES

Maria Dall'Era and Kenneth Kalunian are consultants of Aurinia Pharmaceuticals. Eric Turowski, Vanessa Birardi, Neil Solomons, Simrat Randhawa, and Paola Mina-Osorio are employees and stockholders of Aurinia Pharmaceuticals. Michael Eaddy is a former employee of Xcenda, LLC. Augustina Ogbonnaya and Eileen Farrelly are employees of Xcenda, LLC, which was contracted by Aurinia Pharmaceuticals to assist in the conduct of this study and the writing of this manuscript.

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