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Association of patient copayment and medication adherence in systemic lupus erythematosus

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ABSTRACT

Objective To investigate the association of medication copayment and treatment adherence to hydroxychloroquine and immunosuppressants for SLE.

Methods We conducted a retrospective analysis of health claims data using Optum's de-identified Clinformatics Data Mart Database. Individuals with SLE continuously enrolled for 180 days from 1 July 2010 to 31 December 2019 were included. Adherence was defined as the proportion of days covered ≥80%. Copayment for a 30-day supply of medication was dichotomised as high (≥$10) or low (<$10). We examined the association between copayment and odds of adherence in multivariable-adjusted logistic regression models, including age, sex, race or ethnicity, comorbidities, educational attainment and household income.

Results We identified 12 510 individuals (age 54.2±15.5 years; 88.2% female sex), of whom 9510 (76%) were prescribed hydroxychloroquine and 1880 (15%) prescribed hydroxychloroquine and an additional immunosuppressant (azathioprine, methotrexate or mycophenolate mofetil). Median (IQR) 30-day copayments were $8 (4–10) for hydroxychloroquine, $7 (2–10) for azathioprine, $8 (3–11) for methotrexate and $10 (5–20) for mycophenolate mofetil. High copayments were associated with OR of adherence of 0.61 (95% CI 0.55 to 0.68) for hydroxychloroquine, OR 0.44 (95% CI 0.30 to 0.66) for azathioprine and OR 0.69 (95% CI 0.49 to 0.96) for mycophenolate mofetil. For methotrexate, the association was not significant.

Conclusion In a large, administrative health claims database, we identified that high copayments were associated with reduced adherence to commonly prescribed medications for SLE. Incorporating awareness of the burden of copayments and its consequences into healthcare is essential to promote optimal medication adherence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Medication adherence in SLE is poor and social factors are recognised as potential barriers to optimal adherence.
⇒ Limitations of prior studies include focusing on hydroxychloroquine only and lack of examination of copayment as a contributor to non-adherence.

WHAT THIS STUDY ADDS

⇒ Through this large-sized diverse SLE cohort, we evaluated the association between copayment and adherence to commonly used immunosuppressants. Our analysis was adjusted for several social and economic factors, as well as comorbidities.
⇒ Medication copayment modifies treatment adherence in SLE. Even seemingly small copayments (>$10) may have a significant impact jeopardising adherence to non-biological disease-modifying antirheumatic drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Despite all advances in rheumatology over recent years, the reallocation of resources and efforts to facilitate medication adherence are lagging. Identifying actionable targets for intervention might lay the foundation for improving medication access, and therefore, management of SLE.

INTRODUCTION

Pharmacological treatments for SLE have advanced over the past decades. Medications for this condition can ameliorate its morbidity and are recognised as safe and effective. Hydroxychloroquine has been the backbone of SLE treatment since its US approval in 1955.[1] According to the 2019 European Alliance of Associations for Rheumatology management guidelines, SLE treatment is guided by the universal use of hydroxychloroquine, glucocorticoids and immunosuppressive medications (eg, methotrexate, azathioprine, mycophenolate mofetil).[2] Immunosuppressive medications facilitate disease activity control and achieving remission, as well as enabling glucocorticoid tapering. Immunosuppressive agent selection depends on several factors, most prominently disease manifestations and severity. Methotrexate and azathioprine are usually considered first line in patients who have poor symptom control after hydroxychloroquine and glucocorticoids.[2] Mycophenolate mofetil is efficacious

in renal and non-renal SLE but its cost may limit accessibility to patients.

Despite the known effectiveness and safety of SLE medications, adherence remains a barrier to treatment and thus to improvement in disease outcomes. Adherence to hydroxychloroquine is estimated to range between 15% and 58%.[3–6] In an institutional-based convenience cohort (n=1956), only 58% of individuals achieved adherence ≥80%.[7] Qualitative studies and reviews examining adherence in SLE have identified medication costs, lack of patient acceptance of chronic illness, poor doctor–patient rapport and other factors as obstacles to medication adherence.[8 9] The costs of insurance copayment may present an additional obstacle to adherence, particularly for individuals with limited social resources.

Studies of adherence to medications in SLE have mostly focused on hydroxychloroquine, while other immunosuppressants have had limited examination. We sought to determine the association between copayment magnitude for SLE therapies and adherence to them. We assessed adherence to hydroxychloroquine and immunosuppressive medications including azathioprine, mycophenolate mofetil and methotrexate because of their widespread use in contemporary SLE management. We included relevant social factors—specifically household income and educational attainment—given their potential to contribute towards medication adherence. We hypothesised that higher copayments would be associated with decreased adherence to hydroxychloroquine and immunosuppressive medications in individuals with SLE.

METHODS

Sample selection

We conducted a retrospective analysis of health claims data using Optum's de-identified Clinformatics Data Mart Database (hereafter Clinformatics). Clinformatics is a large US database composed of inpatient, outpatient, emergency department, pharmacy and laboratory health claims. Medical claims include International Classification of Diseases (ICD), Ninth Revision and Tenth Revision codes (ICD-9 and ICD-10); Current Procedural Terminology codes; Healthcare Common Procedure Coding System procedure codes and site of service codes. The database includes commercial and Medicare Advantage enrollees and is geographically diverse across the USA. We followed the Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement for Pharmacoepidemiology checklist.[10]

We identified individuals aged ≥18 years from 1 July 2010 through 31 December 2019, with a diagnosis of SLE and continuous enrolment of at least 180 days (figure 1). We excluded 2020 and 2021 as the COVID-19 pandemic negatively affected access to care and medications for individuals with SLE.[11] Diagnosis of SLE was defined as two claims containing SLE-specific ICD-9/10 codes between 30 and 365 days apart.[12–14] All ICD-9 and ICD-10 administrative codes used are listed in online supplemental table 1. In order to be eligible for study inclusion, participants had to be prescribed at least one medication (hydroxychloroquine, azathioprine, mycophenolate mofetil or methotrexate) or a concomitant of hydroxychloroquine with one immunosuppressant (combination therapy). We specified at least 90 days of dual medication claims to identify combination therapy. The index date was the date of first medication fill. The follow-up period for each medication class spanned the date of first medication claim through either medication discontinuation or end of continuous enrolment, whichever occurred first (figure 2). Discontinuation of medication was defined as 60 or more days without medication and without a subsequent claim. In cases of medication

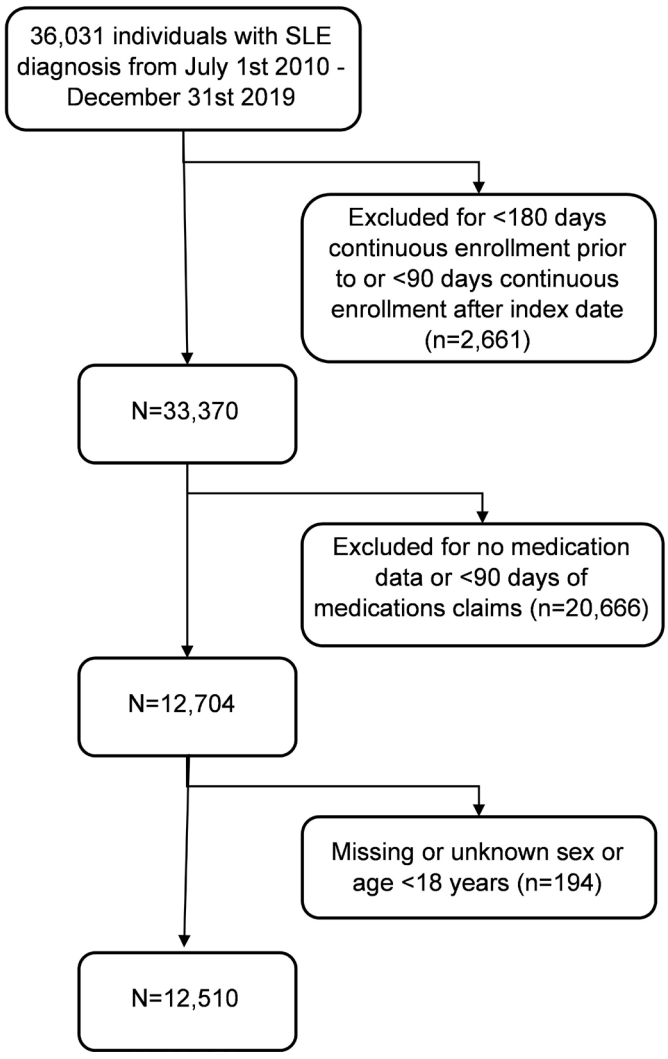

Figure 1 Participant sample selection. Flow chart of the selection of individuals within the cohort. There were 36 031 individuals identified with the diagnosis of SLE from 1 July 2010 until 31 December 2019. Individuals were excluded if they had less than 180 days of continuous enrolment prior to or less than 90 days of continuous enrolment after the index date, no medication data or medication claims for less than 90 days, missing or unknown sex, or age less than 18 years. After exclusions, 12 510 individuals were included for analysis.

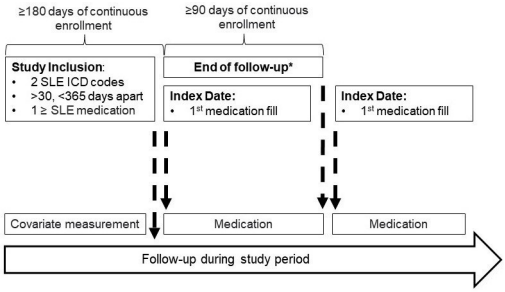

Figure 2 Study design and timeline. For each medication used by the participants included in the study (two SLE-specific ICD-9/10 codes between 30 and 365 days apart; prescribed one or more medications including hydroxychloroquine, azathioprine, mycophenolate mofetil or methotrexate; no exclusion criteria), the follow-up period started with the index date (date of first medication fill) until either medication discontinuation or end of continuous enrolment, whichever occurred first. *End of follow-up: medication discontinuation (≥60 days without the medication) or end of continuous enrolment, whichever occurred first. ICD-9/10, International Classification of Diseases, Ninth Revision/Tenth Revision.

switch (discontinuation and start of a different class), the new medication started would have its adherence assessed separately from the first medication used. There was no established limit for number of medication switch per person. As long as each new medication switched did not meet exclusion criteria (eg, had at least 90 days of medication claim), they were included in the analysis. Individuals were excluded from the cohort if: (a) less than 180 days of continuous enrolment prior to or less than 90 days of continuous enrolment after the index date; (b) no medication data or less than 90 days of medication claims; (c) missing or unknown sex.

Outcomes

We used the individual-average cost per day of medication for each medication class during the follow-up period and multiplied by 30 to determine a mean standardised 30-day copayment for each participant. Then, we described the outcome (adherence, defined as the proportion of days covered (PDC)), which was calculated between the first medication fill and either discontinuation or end of enrolment, whichever occurred first. We assessed adherence from the first medication fill through the end of continuous enrolment. PDC is a validated method to measure medication adherence and it is one of the preferred methodologies in the USA.[15–18] We employed a threshold of 80% to define adherence as the Pharmacy Quality Alliance has designated this value as the level at which medications for chronic diseases, such as rheumatoid arthritis (RA), have a reasonable likelihood of achieving clinical benefit.[19 20] The 80% adherence threshold has been further validated by its association with risk of hospitalisation in chronic illnesses.[21] We consequently dichotomised adherence by PDC ≥80%.[18 19]

Covariates

Age, sex, and race or ethnicity were provided by Clinformatics, which caps age at 89 years to reduce the possibility of identification. Race or ethnicity categories are mutually exclusive. Race or ethnicity in Clinformatics is determined based on public records or by commercial software that uses a validated algorithm to impute race or ethnicity, which is recorded as either Asian, black, Hispanic, white or unknown. The Elixhauser Comorbidity Index conditions, tobacco use, hyperlipidaemia and antiphospholipid syndrome were determined based on the presence of ICD-9/10 codes corresponding to these diagnoses on outpatient or inpatient medical claims. These diagnoses were made prior to the index date. The Elixhauser Comorbidity Index, a validated index that predicts hospital use and mortality, was calculated using a previously described algorithm.[22–24] Educational attainment and household income were categorised and provided by Clinformatics. Educational attainment is derived by combining US census data and the ZIP +4 and categorised as <12th grade, high school, less than bachelor's degree, bachelor's degree or higher, or unknown. Annual household income was determined and categorised as <$40 000; $40 000–60 000; $60 000–100 000 and ≥$100 000. Insurance type is categorised as Medicare or commercial. Deductible contribution is defined as any contribution by individual towards an insurance deductible on SLE medication claims during follow-up versus no contribution. Geographical region was categorised by Clinformatics as described in online supplemental table 2.

Statistical analysis

We summarised the distribution of demographic characteristics for the cohort by each medication. We dichotomised medication copayment as low (<$10 for a 30-day supply) or high (≥$10 for a 30-day supply). We calculated the percentage of the cohort with PDC ≥80% for each medication. Multivariable-adjusted logistic regression models were used to examine the association between medication copay and odds of adherence. We employed a progressive multivariable adjustment using three models adjusting for age, sex, race or ethnicity (model 1); model 1 plus the covariates included in the Elixhauser Comorbidity Index, tobacco use, hyperlipidaemia and antiphospholipid syndrome (model 2); model 2 plus educational attainment, annual household income, insurance type (Medicare vs commercial insurance), deductible contribution (any or none) and geographical region (model 3). As a secondary analysis, we assessed for effect modification of household income on the association between medication copayment in multivariable-adjusted analyses. SAS software V.9.4 was used for statistical analyses.

RESULTS

We identified 36 021 individuals with SLE. Following exclusions for <6 months of continuous enrolment prior to the index date (n=2661), absence of medication data

or <90 days of medication claims (n=20 666), and missing sex (n=194), 12 510 individuals were included in the analysis (figure 1).

Of the 12 510 individuals included in the study, the mean age was 54.2 years (SD ±15.5), and 11 034 (88.2%) were female. The majority of the cohort was composed of white Americans (63.2%), followed by black Americans (14.9%), Hispanic Americans (13.8%), Asian Americans (3.7%) and individuals of unknown race or ethnicity (4.4%) (table 1). In terms of medications, 9510 (76%) were prescribed hydroxychloroquine monotherapy and 1876 (15%) combination therapy. Among immunosuppressive medications, 6.1% of individuals were on azathioprine, 6.7% on mycophenolate mofetil and 4.4% on methotrexate. Median (IQR) 30-day copayments were $8.3 (4–10.7) for hydroxychloroquine, $7 (2.5–10) for azathioprine, $10 (5–20) for mycophenolate mofetil and $7.8 (2.8–11) for methotrexate (table 2). A total of 953 (7.6%) persons in the study were included in at least two regression models, indicating a switch in medication regimen for at least 90 days. Median follow-up was 400 (201–808) days for individuals on hydroxychloroquine, 298 (174–600) days for those prescribed azathioprine, 290 (156–671) days for those prescribed mycophenolate mofetil, 246 (139–455) days for those prescribed methotrexate and 698 (402–1356) days for those prescribed combination therapy.

In our fully adjusted model, the OR of adherence was 0.61 (95% CI 0.55 to 0.68) for higher copayment compared with lower copayment for hydroxychloroquine; 0.44 (95% CI 0.30 to 0.66) and 0.69 (95% CI 0.49 to 0.96) for azathioprine and mycophenolate mofetil, respectively. For methotrexate, we did not observe a significant association between copay and adherence (95% CI 0.57 to 1.59) (table 3). For all medication classes, we observed no significant interaction from annual household income on the association between copay and odds of medication adherence (online supplemental table 3).

DISCUSSION

We employed a large-sized claims database to identify an association between higher medication copayments and lower adherence in individuals with SLE. For hydroxychloroquine, azathioprine and mycophenolate mofetil, the ORs of adherence were 0.61 (95% CI 0.55 to 0.68), 0.44 (95% CI 0.30 to 0.66) and 0.69 (95% CI 0.49 to 0.96), respectively, for copayments above $10 compared with lower copayments. For methotrexate, the association did not reach statistical significance, possibly due to a smaller sample size of patients prescribed this medication (only 4.4% of our cohort). In our analysis of more than 10 000 individuals with SLE, the differences in odds of adherence per high copayments persisted even after adjustments for demographics, several comorbidities and social factors. These results underscore the urgency of ameliorating our patients' access to affordable medications, especially considering that in this study, we examined medications that are the backbone of SLE treatment (hydroxychloroquine) and some that have been scarcely studied in regard to their cost-related adherence (azathioprine, mycophenolate mofetil and methotrexate).

Our research highlights and confirms the high burden of medication costs among individuals with rheumatic diseases. Out-of-pocket costs may pose significant financial strains on persons with RA who need biological disease-modifying antirheumatic drugs (DMARDs).[25–29] In a study of Medicare beneficiaries, coinsurance (percentage paid by patient) for biological DMARDs averaged 29.6%, with a mean out-of-pocket cost of $835/month across all medications examined.[25] A systematic review of six studies evaluating the association between out-of-pocket costs and adherence in RA found that costs negatively affect treatment adherence.[27] Notably, one of the studies showed that increments of $5.5 in weekly out-of-pocket costs were enough to impact adherence.[28] A retrospective cohort of individuals with RA from a national Medicare Advantage and Prescription Drug plan assessed the relationship between out-of-pocket costs and initial prescription, fill and refill of biological DMARDs.[29] This study revealed that 18.2% of the therapy initiators abandoned their prescription after a reversed (non-paid) claim for a biological agent in the 180-day follow-up period. The rate of prescription abandonment further increased with the increase in out-of-pocket costs.[29] In patients with non-rheumatological chronic illnesses, the burden of copayments has been shown to affect treatment adherence and worsen disease outcomes.[30–32] On the other hand, decreasing or eliminating copayments has been associated with increased adherence, especially among low-income individuals.[33]

In a case–control study that assessed sociodemographic and prescription data from an SLE cohort, individuals with a new diagnosis were matched by age, sex, race and geographical residence to those with other chronic diseases. Cases were twice as likely as controls to report cost-related non-adherence and more likely to skip medication doses, take less medications and delay filling their prescriptions due to costs.[34] In our study, even seemingly small increments in the costs of SLE medications had a notable negative association with adherence. A review of SLE adherence studies reiterated fear of side effects, low economic status and medication costs as factors associated with medication non-adherence.[35] Despite the overall adherence in our study being higher than that of many studies in the literature, azathioprine and mycophenolate mofetil presented the lowest adherence (69.5% and 76.3% of individuals on these medications had ≥80% PDC, respectively). A previous Medicaid claims data study reported adherence to azathioprine and mycophenolate mofetil to be as low as <22%,[36] while a small retrospective study of connective tissue diseases (SLE, mixed connective tissue disease, myositis, vasculitis and Sjogren's syndrome were included) found an overall adherence to mycophenolate mofetil of 68.3%.[37] Interestingly, in our study, azathioprine had the largest

Table 1 SLE demographic cohort characteristics

	Cohort (n=12 510)	AZA (n=764)	HCQ (n=9510)	MMF (n=843)	MTX (n=552)	Combination therapy* (n=1880)
Age, mean (SD)	54.2 (15.5)	53.1 (15.1)	54.6 (15.5)	52.0 (15.2)	54.3 (14.3)	52.3 (15.7)
Sex, n (%)						
Female	11 034 (88.2)	652 (85.3)	8495 (89.3)	668 (79.2)	498 (90.2)	1630 (86.7)
Race, ethnicity, n (%)						
White	7910 (63.2)	438 (57.3)	6150 (64.7)	467 (55.4)	347 (62.9)	1137 (60.5)
Asian	457 (3.7)	22 (2.9)	333 (3.5)	43 (5.1)	11 (2)	85 (4.5)
Black	1860 (14.9)	149 (19.5)	1350 (14.2)	151 (17.9)	87 (15.8)	298 (15.9)
Hispanic	1729 (13.8)	113 (14.8)	1271 (13.4)	138 (16.4)	90 (16.3)	277 (14.7)
Unknown	554 (4.4)	42 (5.5)	406 (4.3)	44 (5.2)	17 (3.1)	83 (4.4)
Educational level, n (%)						
High school	3302 (26.4)	220 (28.8)	2487 (26.2)	225 (26.7)	146 (26.5)	491 (26.1)
<Bachelor's degree	6723 (53.7)	416 (54.5)	5081 (53.4)	440 (52.2)	310 (56.2)	1045 (55.6)
≥Bachelor's degree	2065 (16.5)	100 (13.1)	1633 (17.2)	147 (17.4)	83 (15)	278 (14.8)
Unknown	360 (2.9)	26 (3.4)	261 (2.7)	26 (3.1)	11 (2)	58 (3.1)
Household income, n (%)						
<$40 000	3181 (25.4)	206 (27)	2408 (25.3)	213 (25.3)	155 (28.1)	468 (24.9)
$40 000–<60 000	1817 (14.5)	132 (17.3)	1341 (14.2)	121 (14.3)	82 (14.9)	290 (17.4)
$60 000–<100 000	2931 (23.4)	177 (23.2)	2214 (23.3)	193 (23)	129 (23)	467 (24.8)
≥$100 000	3424 (27.4)	175 (22.9)	2666 (28)	229 (27.2)	152 (27.5)	495 (26.3)
Unknown	1157 (9.3)	74 (9.7)	881 (9.3)	87 (10.3)	34 (6.2)	160 (8.5)
Medicare, n (%)	4797 (38.4)	310 (40.6)	3698 (38.9)	291 (34.5)	235 (42.6)	1236 (65.7)
Deductible ($/month, mean, SD)	–	0.05 (0.17)	0.11 (0.42)	0.13 (0.48)	0.09 (0.39)	0.9 (0.33)
Follow-up length† (months; mean, SD)	34.6 (19.8, 59.1)	39.8 (22.8, 66.7)	34.1 (19.1, 58.6)	37.8 (20.8, 64.8)	50.9 (30.9, 80.6)	37.3 (22.7, 60.8)
Glucocorticoid use‡, n (%)	8452 (67.6)	615 (80.5)	6138 (64.5)	637 (75.6)	464 (84.1)	1475 (78.5)
<60 days,	4623 (37.0)	240 (31.4)	3787 (39.8)	202 (24.0)	190 (34.4)	534 (28.4)
≥60 days, low dose	1671 (13.4)	136 (17.8)	1067 (11.2)	190 (22.5)	76 (13.8)	381 (20.3)
≥60 days, moderate dose	2158 (17.3)	239 (31.3)	1284 (13.5)	245 (29.1)	198 (35.9)	560 (29.8)
Clinical characteristics, n (%)						
CKD	1569 (12.5)	116 (14)	1027 (10.8)	1027 (10 .8)	54 (9.3)	222 (11.8)
Hypertension	6932 (55.4)	465 (60.9)	5134 (54)	536 (63.6)	326 (59.1)	1049 (55.8)
Tobacco use	1577 (12.6)	115 (15.1)	1201 (12.6)	93 (11)	87 (15.8)	231 (12.3)
HLD	6350 (50.8)	396 (51.8)	4819 (50.7)	442 (52.4)	300 (54.4)	911 (48.5)
APLS	624 (5)	29 (3.8)	460 (4.8)	54 (6.4)	18 (3.3)	103 (5.5)
Elixhauser comorbidities, median (Q1, Q3)	4 (3, 7)	5 (3, 8)	4 (2, 7)	5 (3, 8)	4 (3, 7)	4 (3, 7)

*Combination therapy: HCQ with another medication (AZA, MMF or MTX).
†Follow-up length refers to the post-index enrolment follow-up in months.
‡Glucocorticoid use: defined here as number of individuals on any dose of prednisone during follow-up period. Low dose: ≤7.5 mg/day of prednisone; moderate dose: 7.5–≤15 mg/day of prednisone.
APLS, antiphospholipid syndrome; AZA, azathioprine; CKD, chronic kidney disease; HCQ, hydroxychloroquine; HLD, hyperlipidaemia; MMF, mycophenolate mofetil; MTX, methotrexate.

magnitude of decrease in odds of adherence for high copayments (56%), and mycophenolate mofetil had the highest absolute copayment (median of $10), as shown in table 2.

Non-adherence to treatment in SLE has been linked to increased emergency department visits and hospitalisation, even after consideration of sociodemographic factors and comorbidities.[38] In a patient interview-based

Table 2 Proportion of days covered (PDC) and copay by medication

	HCQ (n=9510)	AZA (n=764)	MMF (n=843)	MTX (n=552)	Combination therapy* (n=1880)
Copayment†, median (Q1, Q3)	8.3 (4, 10.7)	7 (2.5, 10)	10 (5, 20)	7.8 (2.8, 11)	8.6 (4, 11.6)
PDC, median % (Q1, Q3)	93 (81, 99)	92 (81, 98)	90 (76, 97)	92 (83, 99)	93 (85, 97)
PDC ≥80%, n (%)	7287 (76.6)	583 (76.3)	586 (69.5)	447 (81)	1585 (84.3)
Copay ≥$10/month‡, n (%)	3763 (39.6)	279 (34.1)	503 (54.4)	228 (39.4)	792 (42.1)

*Combination therapy: HCQ with another medication (AZA, MMF or MTX).
†Indicates median (Q1, Q3) in dollars per 30 days.
‡Number (and %) of individuals with monthly copayment >$10.
AZA, azathioprine; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate.

prospective study (n=982), patients who reported forgetting medications 'all the time' were more likely to have emergency room visits than those forgetting 'some' or 'most of the time'.[39] In a US paediatric cohort study, claims data-derived adherence to hydroxychloroquine and immunosuppressants was predictive of future hospitalisation. This study also used PDC ≥80% as measure for adherence.[40] A longitudinal cohort with 332 individuals with SLE evaluated the association between patient medication cost concerns (encompassing difficulty affording medications, delaying refills, requesting lower-cost alternatives, etc) and patient-reported outcomes. In this study, the group of patients that expressed medication cost concerns had worse disease activity, depression symptoms, pain, fatigue and poorer sleep compared with the group without medication cost concerns, and this difference persisted over time.[41] In Canada, adherence to antimalarials in SLE was shown to decrease the risk of death by 83% and 42% compared with those with limited adherence.[42] Notably, this study

Table 3 OR of medication adherence (PDC)* by copay per covariable adjustment by models

	Copayment ≥$10/month vs <$10			
	OR	Lower CI	Upper CI	P value
Model 1				
AZA (n=764)	0.53	0.37	0.75	0.0004
HCQ (n=9510)	0.59	0.53	0.65	<0.0001
MMF (n=843)	0.76	0.57	1.03	0.08
MTX (n=552)	1.03	0.66	1.61	0.90
Combination therapy (n=1880)	0.75	0.58	0.97	0.03
Model 2				
AZA (n=764)	0.51	0.36	0.73	0.0002
HCQ (n=9510)	0.60	0.54	0.66	<0.0001
MMF (n=843)	0.76	0.56	1.03	0.07
MTX (n=552)	1.08	0.69	1.70	0.73
Combination therapy (n=1880)	0.75	0.58	0.97	0.03
Model 3				
AZA (n=764)	0.44	0.30	0.66	<0.0001
HCQ (n=9510)	0.61	0.55	0.68	<0.0001
MMF (n=843)	0.69	0.49	0.96	0.03
MTX (n=552)	0.95	0.57	1.59	0.85
Combination therapy (n=1880)	0.73	0.55	0.97	0.03

Model 1: adjusted by age, sex, and race or ethnicity.
Model 2: adjusted by model 1 variables, Elixhauser comorbidities, tobacco use, HLD and antiphospholipid syndrome.
Model 3: adjusted by model 2 variables, annual household income, educational attainment, insurance type, deductible contribution and geographical region.
*Medication adherence is defined as PDC ≥80%.
AZA, azathioprine; HCQ, hydroxychloroquine; HLD, hyperlipidaemia; MMF, mycophenolate mofetil; MTX, methotrexate; PDC, proportion of days covered.

used a stricter definition of adherence than ours (PDC >90%).

Our study identified that increased copayments are associated with lower odds of adherence. Mechanisms that may explain our findings pertain to both patients' financial insecurity and physicians' orientation toward the financial obstacles to treatment. Individuals with SLE suffer from a high comorbidity burden,[43] and often are affected by polypharmacy and its associated costs.[44] The burden of polypharmacy which frequently accompanies SLE treatment may exacerbate financial strain due to prescription costs. Concurrently, physicians have limited ability to estimate their patients' drug costs. In a survey of physicians practising in New York, 80% of respondents were unaware of the costs of medications, and 55% inaccurately estimated prices for commonly used drugs.[45] In another survey that included 131 randomly selected rheumatologists, participants had difficulty estimating out-of-pocket costs for patients even when given adequate information about their patients' insurance plans.[46] On the provider level, there is room for improvement in awareness of drug costs, with more engagement in patient–doctor discussions regarding medication cost concerns.

Our study contributes to the body of scholarship which has demonstrated the financial costs of SLE. Prior literature has reported the significant financial toll on the healthcare system.[13 47–49] We now demonstrate how patient-level costs may modify medication adherence, fundamental for maintaining treatment and reducing disease morbidity and adversity. Importantly, studies have focused on the costs of newer medications such as biologics; however, in our study, we show the impact of costs on the usage of non-biological immunosuppressive medications for SLE, which are usually considered first line of the disease treatment. Targeted healthcare policies to lower patient cost-sharing are essential and may translate to increased medication adherence and improved health outcomes.[30] Despite the available data demonstrating the effects of adherence on healthcare utilisation, costs and possibly patient outcomes, guidelines do not yet consider medication prices as a component of treatment choice.[2]

The strengths of our study include using a large and diverse cohort of individuals with SLE, including hydroxychloroquine, azathioprine, methotrexate and mycophenolate mofetil, along with several relevant covariates. As was shown by another claims data study, concordance between adherence to hydroxychloroquine and adherence to immunosuppressants is only moderate, demonstrating the importance of considering other SLE therapies individually.[40]

Our study has some important limitations. Foremost is the potential for misclassification that is inherent to using claims data. To reduce potential misclassification, we employed ICD-9/10 codes specific to SLE with the additional stipulation that individuals are prescribed medications for SLE. Second, while our cohort is large sized with geographical viability, the generalisability is limited by including only individuals with insurance. We expect challenges to medication access would be all the more challenging in the USA for those with chronic rheumatological diseases and who lack health insurance. Third, we used PDC to quantify adherence. We recognise that PDC accounts for claims from filling prescriptions but does not measure actual medication usage and ingestion. Observed therapy is both impractical and not feasible when using administrative claims data. Fourth, we observed small sample sizes for analyses of azathioprine, methotrexate and mycophenolate mofetil individually. Finally, we are unable to exclude residual confounding from unmeasured factors that may contribute towards the association between medication copayment and adherence, such as disease severity or other barriers not measured by administrative data.

In conclusion, we used a large, administrative health claims database to determine that increased copayments are associated with reduced adherence to hydroxychloroquine and immunosuppressive medications in individuals with SLE. Incorporating awareness of the burden of copayments and its consequences into medication adherence is essential for improving medication access in individuals with SLE, and has the potential to improve outcomes and decrease healthcare utilisation in a complex and socially costly chronic disease.

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Contributors JWM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and serves as guarantor. Concept and design—RLS, GMS and JWM. Acquisition, analysis or interpretation of data—RLS, GMS, SES and JWM. Drafting of the manuscript—RLS, GMS, SES and JWM. Critical revision of the manuscript for important intellectual content—RLS, GMS, SES and JWM. Statistical analysis—GMS. Obtained funding—JWM. Administrative, technical or material support—GMS. Supervision—SES and JWM.

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