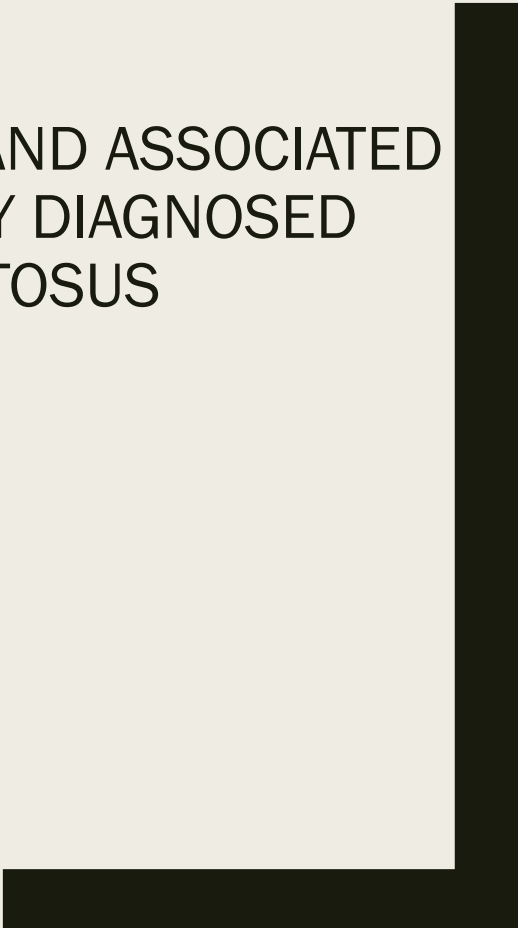




LONGITUDINAL TREATMENT PATTERNS AND ASSOCIATED
OUTCOMES IN PATIENTS WITH NEWLY DIAGNOSED
SYSTEMIC LUPUS ERYTHEMATOSUS

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Systemic Lupus Erythematosus

- SLE is a chronic autoimmune disease that affects multiple organs including the heart, lung, kidney, joint, and the nervous system
- Standard therapies for SLE include corticosteroids, antimalarial agents, non-steroidal anti-inflammatory drugs, cytotoxic agents, and immunosuppressive/ immunodulatory agents

Systemic Lupus Erythematosus

- The objectives of this study are (1) to describe longitudinal treatment patterns in newly diagnosed SLE patients from a multi-payer U.S. claims database and (2) to estimate association of longitudinal treatment patterns with clinical and economic outcomes

Methods: Defining Newly Diagnosed SLE Cases

- This retrospective cohort analysis followed newly diagnosed SLE patients for 4 years after first diagnosis in MarketScan commercial database
- The earliest date of a medical claim with a diagnosis of SLE (710.0x) from January 1, 2002 through March 31, 2008 was defined as the index date. Subjects were required to be ≥ 18 years old at index date, had continuous medical and pharmacy benefits for 12 months prior to index without SLE diagnosis and 48 months after index, with ≥ 1 SLE-related inpatient claim or ≥ 2 office or emergency room visits with an SLE diagnosis at least 30 days apart during the first 12 months after index. At least one SLE diagnosis on or during 12 months after index must be made by a rheumatologist, dermatologist, nephrologist, or neurologist

Methods:

Cluster Analysis

- A disjoint k-means cluster analysis was performed to identify longitudinal treatment patterns over 4 years after SLE diagnosis
- Annual number of prescriptions for each of the 4 years are used as input variables
- Clustering criterion was based on within cluster sum of squares computed from the input variables

Methods:

Cluster Analysis

- Total number of prescriptions of all corticosteroids was summed up for each patient in each of the 4 years after index
- Other SLE therapies must have at least 0.05 mean number of prescriptions in each of the 4 years to be included in the analysis
- No standardization of input variables is needed

Methods: Cluster Analysis

- SAS procedure FASTCLUS with random initial centroids was employed
- An iterative process was adopted to choose the best number of clusters based on clustering performance including the minimized overall distance to cluster centroids as well as clinical and practical judgment.
- The k-means cluster analysis with random initial centroids was run 10,000 times

Methods: Regression of Clinical and Economic Outcomes

- Clinical and economic outcomes were summarized over the 4-year follow-up period
 - *Ever had severe SLE*
 - *Number of severe flares*
 - *Number of all-cause hospital and ED visits*
 - *Number of all-cause office and outpatient visits*
 - *Total all-cause hospital and ED costs*
 - *Total all-cause office and outpatient visit costs*
 - *Total all-cause outpatient prescription drug costs*
 - *Total all-cause medical care costs*

- Association with the identified treatment clusters was estimated with:
 - *Poisson and negative binomial regression models for count variables*
 - *generalized linear models with the log link and gamma distribution for cost outcomes;*
 - *logistic regression models for binary variables*
 - *controlling for age, sex, health plan type, geographic region, CCI at baseline, and management primarily by a specialist versus a PCP post baseline*

Results: Sample

- 1,611 newly diagnosed SLE patients were identified with 91% being female, a mean age of 44.5 years (SD: 9.5), and a mean CCI score of 1.0 (SD: 1.3)
- 56.2% (n=905) of patients were primarily managed by a specialist, and 43.8% (706) by PCPs (Table 1)

Table 1: Baseline Characteristics of Newly Diagnosed SLE Patients

	Complete study sample (n=1,611)	Patients managed primarily by specialists (n=905)	Patients managed primarily by PCPs (n=706)	P value, patients primarily managed by specialists versus PCPs ^a
Female, n (%)	1,472 (91.4%)	827 (91.4%)	645 (91.4%)	0.99
Mean age, years (SD)	44.5 (9.5)	44.2 (9.5)	44.9 (9.5)	0.14
Age group, n (%)				
≤ 40 years	523 (32.5%)	309 (34.1%)	214 (30.3%)	0.21
41–50 years	574 (35.6%)	320 (35.4%)	254 (36%)	
≥ 50 years	514 (31.9%)	276 (30.5%)	238 (33.7%)	
Mean CCI (SD)	1.0 (1.3)	1.0 (1.3)	1.0 (1.4)	0.95
Health plan type, n (%)				
Comprehensive	209 (13.0%)	107 (11.8%)	102 (14.5%)	0.26
HMO	253 (15.7%)	137 (15.1%)	116 (16.4%)	
PPO	889 (55.2%)	502 (55.5%)	387 (54.8%)	
POS	53 (3.3%)	33 (3.7%)	20 (2.8%)	
Others ^b	207 (12.9%)	126 (13.9%)	81 (11.5%)	
Region, n (%)				<0.0001
Northeast	168 (10.4%)	109 (12.0%)	59 (8.4%)	
North central	327 (20.3%)	160 (17.7%)	167 (23.7%)	
South	879 (54.6%)	540 (59.7%)	339 (48.0%)	
West	222 (13.8%)	83 (9.2%)	139 (19.7%)	
Unknown	15 (0.9%)	13 (1.4%)	2 (0.3%)	

* CCI, Charlson comorbidity index; HMO, health maintenance organization; PCP, primary care providers; POS, point of service; PPO, preferred provider organization; SD, standard deviation

Results: SLE Treatments

- Corticosteroids, hydroxychloroquine, mycophenolate mofetil, azathioprine, and methotrexate were included in the cluster analysis
- All other SLE therapies (chloroquine, quinacrine, cyclophosphamide, cyclosporine, leflunomide, and all biologics) were excluded because of very low use (<0.05 annual mean number of prescriptions in each of the four years after diagnosis)

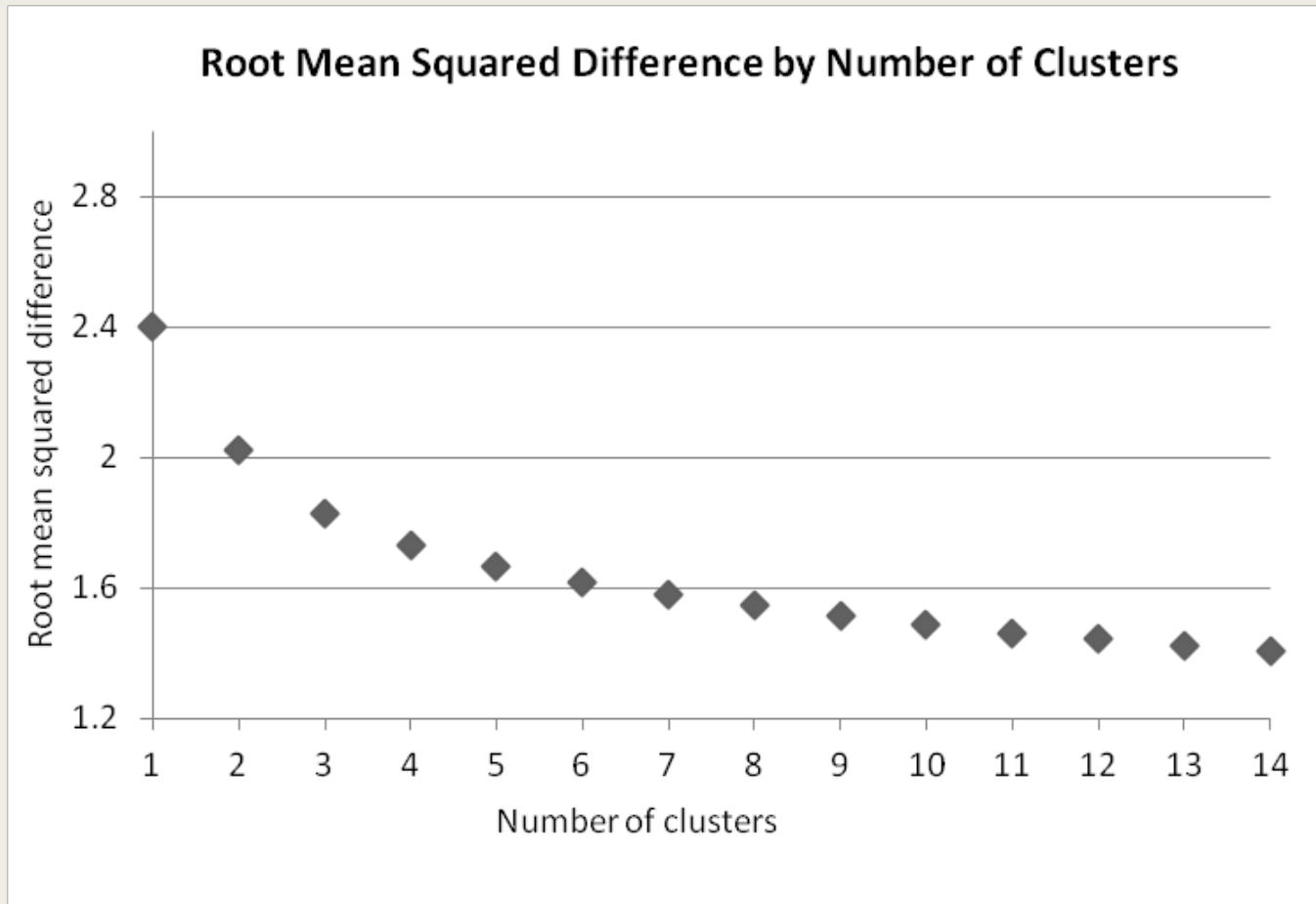
Results: SLE Treatments

Table 2: Mean (SD) number of prescriptions and percent of patients with ≥ 1 prescriptions and mean days of supply* and mean daily dose* by year (n=1,611 patients)

	Use (% of study population)	Mean number of scripts (SD)	Mean days of supply ^a (SD)	Mean daily dose, ^{a,b} mg (SD)
Year 1				
Corticosteroids	60.2	2.8 (3.6)	30.4 (23.2)	18.5 (26.3)
Hydroxychloroquine	64.1	4.3 (4.1)	40.7 (23.6)	377.3 (107.3)
MMF	5.2	0.3 (1.3)	38.7 (23.0)	1812.4 (750.1)
Azathioprine	7.4	0.4 (1.7)	38.6 (23.0)	92.2 (36.7)
Methotrexate	11.9	0.7 (2.5)	36.5 (23.3)	2.6 (2.1)
Year 2				
Corticosteroids	51.4	2.4 (3.4)	31.8 (23.8)	15.4 (24.4)
Hydroxychloroquine	55.9	3.9 (3.9)	43.2 (25.6)	378.4 (89.0)
MMF	5.3	0.3 (1.5)	42.1 (26.0)	1822.0 (742.8)
Azathioprine	6.2	0.4 (1.7)	38.4 (21.4)	101.1 (41.3)
Methotrexate	9.7	0.7 (2.6)	39.7 (24.9)	3.1 (9.6)
Year 3				
Corticosteroids	49.0	2.3 (3.3)	33.3 (25.4)	14.5 (17.5)
Hydroxychloroquine	52.0	3.6 (3.9)	44.7 (26.2)	374.0 (83.8)
MMF	5.4	0.3 (1.4)	43.5 (26.2)	1719.9 (725.1)
Azathioprine	6.0	0.4 (1.7)	42.0 (23.8)	99.1 (39.1)
Methotrexate	9.6	0.6 (2.1)	41.4 (25.4)	3.2 (10.6)
Year 4				
Corticosteroids	49.0	2.3 (3.2)	31.7 (24.8)	14.5 (17.5)
Hydroxychloroquine	49.0	3.4 (3.7)	46.2 (27.0)	374.0 (83.8)
MMF	5.7	0.4 (1.6)	45.9 (27.3)	1719.9 (725.1)
Azathioprine	5.5	0.4 (1.7)	42.5 (24.5)	99.1 (39.1)
Methotrexate	8.6	0.6 (2.1)	41.6 (24.7)	3.2 (10.6)

* mean days of supply and mean daily dose were averaged across prescriptions of the specific drug rather than all of the patients

Results: Choosing Number of Clusters



Results: Clusters of Longitudinal Treatments

- Ten treatment clusters were identified (Table 3). Over the 4-year period, the most common treatment cluster was minimally-treated patients (42.8%).
- Corticosteroid monotherapy, hydroxychloroquine monotherapy and corticosteroid/hydroxychloroquine combination therapy with persistent and non-persistent use were received by 11.2%, 34.0%, and 7.8% of patients, respectively.
- Methotrexate or azathioprine with corticosteroids/hydroxychloroquine were received by 4.2% of patients.
- Changes in therapy other than discontinuations were rare.*

* Although no major patterns of therapy changes other than discontinuation were identified, there were numerous small changes of individual therapies which were not clustered into major patterns.

Results: Clusters of Longitudinal Treatments

Table 3: Longitudinal Treatment Patterns Identified with 10 Clusters

Cluster	n (%)		Mean number of prescriptions: yr 1					Mean number of prescriptions: yr 2					Mean number of prescriptions: yr 3					Mean number of prescriptions: yr 4					Interpretations
			CS	HCQ	MMF	AZA	MTX	CS	HCQ	MMF	AZA	MTX	CS	HCQ	MMF	AZA	MTX	CS	HCQ	MMF	AZA	MTX	
1	690	42.8%	0.5	0.5	0.0	0.1	0.1	0.4	0.3	0.0	0.0	0.1	0.4	0.2	0.1	0.0	0.1	0.4	0.3	0.1	0.0	0.1	Minimally treated throughout 4 years
2	35	2.2%	11.0	2.2	0.7	0.7	2.1	12.3	1.5	1.1	0.7	1.5	13.3	1.0	1.2	1.1	1.4	13.1	1.5	1.2	1.1	0.8	Corticosteroids only: persistent high users
3	145	9.0%	4.8	1.0	0.8	0.2	1.1	4.4	0.6	1.0	0.2	0.8	3.5	0.5	0.7	0.2	0.5	3.3	0.3	0.7	0.2	0.4	Corticosteroids only: moderate users with slow reduction
4	152	9.4%	1.9	9.4	0.3	0.1	0.2	0.9	10.3	0.2	0.1	0.2	1.0	10.3	0.2	0.2	0.2	1.1	9.1	0.2	0.2	0.2	HCQ only: persistent high users
5	240	14.9%	1.2	3.2	0.1	0.1	0.2	1.0	3.7	0.2	0.1	0.1	0.9	4.0	0.2	0.1	0.2	0.9	3.8	0.3	0.1	0.2	HCQ only: persistent moderate users
6	156	9.7%	1.8	8.9	0.2	0.1	0.2	1.2	5.1	0.1	0.0	0.1	0.8	2.8	0.1	0.0	0.1	1.1	2.0	0.1	0.1	0.2	HCQ only: non-persisters
7	50	3.1%	9.6	9.4	1.2	1.3	0.9	10.0	10.1	1.5	1.5	0.8	9.4	10.2	1.7	1.2	1.0	7.9	9.1	1.7	1.3	0.7	Corticosteroids+HCQ: persistent high users
8	76	4.7%	9.7	6.8	0.5	0.6	0.7	6.1	5.1	0.4	0.4	0.4	5.4	4.1	0.2	0.1	0.5	4.8	3.4	0.4	0.2	0.4	Corticosteroids+HCQ: non-persisters
9	27	1.7%	3.9	4.3	0.3	0.0	9.4	3.8	4.1	0.1	0.0	11.1	2.3	3.7	0.0	0.0	8.7	2.9	3.4	0.1	0.0	7.6	Methotrexate moderate users with some corticosteroids and HCQ
10	40	2.5%	3.3	3.1	0.2	6.5	0.1	3.2	2.4	0.0	7.0	0.3	3.0	2.8	0.1	6.5	0.2	2.7	2.2	0.5	5.5	0.2	Azathioprine moderate users with some corticosteroids and HCQ

* CS= corticosteroids, HCQ=hydroxychloroquine, MMF=mycophenolate mofetil, MTX=methotrexate, AZA=azathioprine

Results: Outcomes across Clusters

Table IV. Patient characteristics and cumulative clinical and economic outcomes by longitudinal treatment cluster in patients with incident SLE (N = 1611).

Cluster	Baseline Characteristics				Mean (SD) No. of Visits			Mean (SD) Costs, \$			
	Mean (SD) Age, y	Female, %	Mean (SD) CCI	Severe SLE Disease Criteria Met at Least Once, No. (%)	Mean (SD) No. of Severe Flares	Hospital and ED	Office and Outpatient*	Hospital and ED	Office and Outpatient	Prescription Drugs	Medical Care
All patients	44.5 (9.5)	91.4	1.0 (1.3)	198 (12.3)	0.6 (1.7)	2.6 (4.2)	103.2 (76.5)	29,170 (93,198)	9,962 (13,881)	12,164 (20,772)	51,295 (104,204)
Cluster											
1. Minimally treated	44.8 (9.1)	93.2	0.9 (1.3)	50 (7.3)	0.3 (0.8)	2.4 (3.8)	98.5 (76.1)	30,107 (103,437)	9,276 (14,241)	6,531 (12,380)	45,914 (111,110)
2. CS only: persistent heavy users	41.3 (9.7)	91.4	1.1 (1.2)	10 (28.6)	2.7 (7.0)	5.7 (8.8)	132.3 (89.3)	56,183 (168,319)	12,678 (20,102)	23,496 (29,085)	92,357 (193,462)
3. CS only: moderate users with slow reduction	45.6 (9.9)	91.0	1.3 (1.5)	49 (33.8)	1.5 (2.4)	4.9 (6.5)	130.2 (74.4)	58,258 (148,320)	13,701 (12,162)	20,654 (22,084)	92,614 (157,930)
4. HCQ only: persistent heavy users	43.3 (9.5)	88.2	0.8 (1.1)	16 (10.5)	0.4 (0.9)	1.8 (3.5)	95.3 (62.4)	15,159 (46,409)	8,908 (9,092)	13,721 (17,788)	37,788 (55,787)
5. HCQ only: persistent moderate users	44.9 (8.8)	91.3	0.9 (1.3)	22 (9.2)	0.3 (0.9)	1.9 (2.9)	99.4 (90.6)	17,368 (43,905)	9,143 (11,530)	14,866 (26,123)	41,377 (57,580)
6. HCQ only: nonpersisters	45.6 (9.1)	93.6	1.0 (1.5)	12 (7.7)	0.3 (0.7)	1.6 (2.0)	87.2 (47.3)	18,904 (42,764)	8,573 (10,551)	14,520 (34,251)	41,997 (63,743)
7. CS + HCQ: persistent heavy users	40.6 (10.6)	90.0	1.1 (1.4)	11 (22.0)	1.2 (2.3)	2.6 (3.2)	99.8 (54.2)	26,714 (42,769)	7,598 (5,558)	13,313 (12,144)	47,625 (48,361)
8. CS + HCQ: nonpersisters	47.0 (8.7)	82.9	1.3 (1.2)	15 (19.7)	1.0 (2.5)	2.6 (4.7)	124.9 (87.3)	43,524 (110,916)	14,193 (22,602)	17,221 (16,298)	74,937 (132,031)
9. MTX moderate users with some CS and HCQ	45.6 (9.1)	88.9	1.7 (1.9)	3 (11.1)	0.5 (0.9)	3.7 (5.8)	128.9 (106.6)	25,750 (57,241)	11,062 (13,727)	20,436 (20,038)	57,248 (75,763)
10. AZA moderate users with some CS and HCQ	47.2 (10.0)	85.0	1.3 (1.3)	10 (25.0)	1.1 (1.7)	3.0 (3.4)	121.1 (67.5)	26,117 (41,131)	14,358 (24,563)	20,686 (18,402)	61,161 (73,230)

AZA = azathioprine; CCI = Charlson comorbidity index; CS = corticosteroid; ED = emergency department; HCQ = hydroxychloroquine; MTX = methotrexate; SLE = systemic lupus erythematosus.

*Visits include independent laboratory (65%), end-stage renal disease facility (11%), patient home (14%), ambulatory surgical center (4%), and other (6%).

Results: Regression

Table V. Model estimates of association of longitudinal treatment patterns with clinical and economic outcomes in patients with incident SLE (N = 1611).

Characteristic	Severe SLE Criteria Met at Least Once [†]	No. of Severe Flares [‡]	No. of Hospital and ED Visits [‡]	No. of Office and Outpatient Visits [§]	Total Hospital and ED Costs [¶]	Total Office and Outpatient Visit Costs [¶]	Total Prescription Drug Costs [¶]	Total Medical Care Costs [¶]
Age group (ref, 18–40 y)								
>40–<50 y	1.29	0.98	1.03	1.12**	1.23	1.25**	1.49*	1.36***
≥50 y	0.86	0.91	0.91	1.16**	1.22	1.14*	1.53***	1.29**
Sex (ref, male)								
Female	0.84	0.87	0.92	1.22***	0.91	1.18*	1.32**	1.05
Health plan type (ref, PPO)								
Comprehensive	1.20	0.92	0.98	0.98	0.88	1.13	1.21*	1.03
HMO	1.39	1.17	1.16	1.00	0.67*	0.98	0.84	0.76*
Other	1.54	1.37	1.06	1.14***	0.98	1.33***	1.19	1.14
POS	1.03	1.17	0.89	0.99	0.76	0.82	0.83	0.78
Geographic region (ref, South)								
North Central	1.32	1.20	0.98	1.01	0.84	1.06	0.99	0.98
Northeast	0.74	0.73	1.55***	1.10***	0.79	1.08	0.95	0.89
West	0.72	0.65*	0.86	1.09**	1.20	1.29***	1.27**	1.11
Unknown	1.33	1.17	1.07	0.89***	0.51	0.85	1.0	0.78
CCI (ref, 0)								
1	1.50*	1.40*	1.79***	1.24***	1.34*	1.32**	1.43***	1.67***
2	1.22	1.61**	2.32***	1.43***	2.13**	1.82***	1.98***	2.30***
3	2.38**	2.22**	2.89***	1.72***	4.43***	2.54***	2.00***	4.34***
≥4	2.42**	3.35***	4.20***	1.76***	3.29***	2.73***	1.84***	3.90***
Primarily managed by (ref, PCP)								
Specialist	0.86	0.77*	0.71***	0.87**	0.93	0.80***	0.85**	0.82**
Treatment pattern (ref, 1. Minimally treated)								
2. CS only: persistent heavy users	4.80***	8.97***	2.19***	1.39***	0.95	1.31	2.49***	1.73**

(continued)

Results: Regression

Table V. (continued).

Characteristic	Severe SLE Criteria Met at Least Once [†]	No. of Severe Flares [‡]	No. of Hospital and ED Visits [‡]	No. of Office and Outpatient Visits [§]	Total Hospital and ED Costs [¶]	Total Office and Outpatient Visit Costs [¶]	Total Prescription Drug Costs [¶]	Total Medical Care Costs [¶]
3. CS only: moderate users with slow reduction	5.87***	4.86***	1.81***	1.23**	1.74**	1.49***	1.90***	1.99***
4. HCQ only: persistent heavy users	1.44	1.24	0.76*	1.00	0.63*	1.09	1.57**	0.98
5. HCQ only: persistent moderate users	1.17	1.10	0.83	1.01	0.82	1.10	1.46**	1.05
6. HCQ only: nonpersisters	0.96	0.86	0.72**	0.88**	0.77	0.96	1.41**	1.04
7. CS + HCQ: persistent heavy users	3.40**	4.31***	1.01	1.01	0.96	0.90	1.55**	1.22
8. CS + HCQ: nonpersisters	2.87**	3.15***	0.94	1.21**	1.60	1.37***	1.65***	1.59**
9. MTX moderate users with some CS and HCQ	1.42	1.34	1.33	1.27**	0.71	1.04	1.95**	1.10
10. AZA moderate users with some CS and HCQ	3.91**	3.29**	1.12	1.16**	0.85	1.28	1.82**	1.27

AZA = azathioprine; CCI = Charlson comorbidity index; CS = corticosteroid; ED = emergency department; HCQ = hydroxychloroquine; HMO = health maintenance organization; MTX = methotrexate; PCP = primary care provider; POS = point of service; PPO = preferred provider organization; SLE = systemic lupus erythematosus.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[†]Logistic regression (odds ratio).

[‡]Negative binomial regression (incidence rate ratio).

[§]Poisson regression (incidence rate ratio).

[¶]Generalized linear model (ratio of costs).

Conclusions

- Newly diagnosed SLE patients showed distinct patterns of treatment pathways over the first 4 years after diagnosis.
- Close to half of them were not actively treated and the rest were treated with corticosteroids, hydroxychloroquine and immunosuppressants with different combinations, intensity and persistence.
- 11.2% received corticosteroid monotherapy. Only a very small proportion (4.2%) were consistently treated with immunosuppressants.
- Patients mostly stayed on initial treatment or discontinued the initial treatment over 4 years after initial diagnosis.

Conclusions

- Clinical and economic outcomes are poorest with corticosteroid monotherapy but may improve with the additional of hydroxychloroquine and/or an immunosuppressive agent
- A large proportion of SLE care is provided by nonspecialists despite the potential benefits of involving a specialist