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Original article

Disease severity, flares and treatment patterns in adults with systemic lupus erythematosus in the UK: a real-world observational retrospective cohort analysis

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Abstract

Objectives. The aim was to characterize disease severity, clinical manifestations, treatment patterns and flares in a longitudinal cohort of adults with SLE in the UK.

Methods. Adults with SLE were identified in the Clinical Practice Research Datalink–Hospital Episode Statistics database (1 January 2005–31 December 2017). Patients were required to have ≥12 months of data before and after the index date (earliest SLE diagnosis date available). SLE disease severity and flares were classified using adapted claims-based algorithms, which are based on SLE-related conditions, medications and health-service use.

Results. Of 802 patients, 369 had mild, 345 moderate and 88 severe SLE at baseline. A total of 692 initiated treatment in the first year after diagnosis. Five hundred and fifty-seven received antimalarials, 203 immunosuppressants and 416 oral CSs. Information on biologic use in hospitals was unavailable. The mean (S.D.) time to initiating any medication was 177 (385.3) days. The median time to first flare was 63 days (95% CI: 57, 71). At least one flare was experienced by 750 of 802 patients during follow-up; the first flare was mild for 549 of 750, moderate for 116 of 750 and severe for 85 of 750. The mean (S.D.) annual overall flare rate (year 1) was 3.5 (2.5). A shorter median time to first flare was significantly associated with moderate/severe disease ($P < 0.001$) and clinical manifestations ($P < 0.001$).

Conclusion. Our findings suggest some delay in the initiation of SLE treatment. Most patients experience a flare within 2 months of diagnosis. Early treatment might delay or reduce the severity of the first SLE flare and might translate to slower disease progression, lower accrual of organ damage and better outcomes.

Key words: SLE and autoimmunity, epidemiology, immunosuppressants, DMARDs, quality of health care

Key messages

- This is a longitudinal study to describe disease severity and activity in UK SLE patients over 6 years.
- SLE patients, on average, initiate treatment 6 months after diagnosis.
- There may be opportunities to change SLE management and improve patient outcomes.

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CLINICAL SCIENCE

Introduction

SLE is a systemic autoimmune disease characterized by autoantibody presence and immune complex deposition in affected tissues [1]. SLE can involve multiple organ systems, resulting in diverse clinical manifestations that range from fatigue and mild skin rash to end-stage renal failure [2]. Patients with SLE are at increased risk of developing comorbid conditions, including those involving the renal, cerebrovascular, hepatic, gastrointestinal and neurological organ systems [3–5]. All-cause mortality in SLE is >3-fold compared with the general population [6, 7].

The clinical course of SLE is marked by periods of remission, which may be spontaneous or induced by treatment, interspersed by periods of increased disease activity known as SLE flares [8]. SLE flare episodes usually require consideration for changes in treatment or increased medication doses of existing treatment [9]. Flares have been associated with an increased risk of organ damage [10], and ∼50% of all patients with SLE experience some form of organ damage within 10 years of diagnosis [11]. The use of oral CSs for SLE treatment and management of flares is associated with side effects, including the risk of contributing to chronic organ damage and infection. Recent SLE treatment guidelines recommend the lowest possible oral CS doses followed by taper or discontinuation when decreased flare frequency and severity is achieved, and other immunosuppressive agents show benefit [2, 12].

There are limited longitudinal data describing real-world SLE disease characteristics and flares in the UK. Our study aimed to characterize disease severity, clinical manifestations, treatment patterns and flares in a longitudinal cohort of patients with new-onset SLE in the UK.

Methods

Study design

We conducted an observational, retrospective cohort study of adult patients with new-onset SLE in the UK identified in the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES)–linked health-care administrative databases and Office for National Statistics mortality files from 1 January 2005 to 31 December 2017. Patients were required to have ≥12 months of SLE disease-free time before the index date (date of first SLE diagnosis) and ≥12 months of follow-up (up to 31 December 2017) (Fig. 1A). Approval for this study was granted by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency on 8 March 2018 (CPRD00023132 PROTOCOL 17_281R).

Data sources

Data were sourced from three routinely obtained and linked data sources in the UK. The CPRD database used in this study was CPRD GOLD, contributed to by general practices using Vision software and collected since 1987. CPRD GOLD contains anonymous longitudinal medical records of >14 million patients, is broadly representative of the UK population in terms of age and sex, and has information on demographics, diagnoses and primary health-care utilization, including outpatient prescription medications [13, 14], and has been shown in a number of validation studies to be generally of high quality [15, 16]. The CPRD primary care database has been used previously to describe the epidemiology of SLE in the UK [17–28].

These primary care data were linked to secondary care information [hospital admissions, and the International Classification of Diseases, Tenth Revision (ICD-10) for the coding of diagnosis and type of admission] identified in the HES database. Death registration data, to identify mortality and causes of death, were obtained from the Office for National Statistics. CPRD GOLD linkage data include patients from 416 practices, covering ∼50% of contributing CPRD GOLD practices in the UK. All data were anonymized, and linkage, by patient identifiers held by CPRD, was conducted by CPRD.

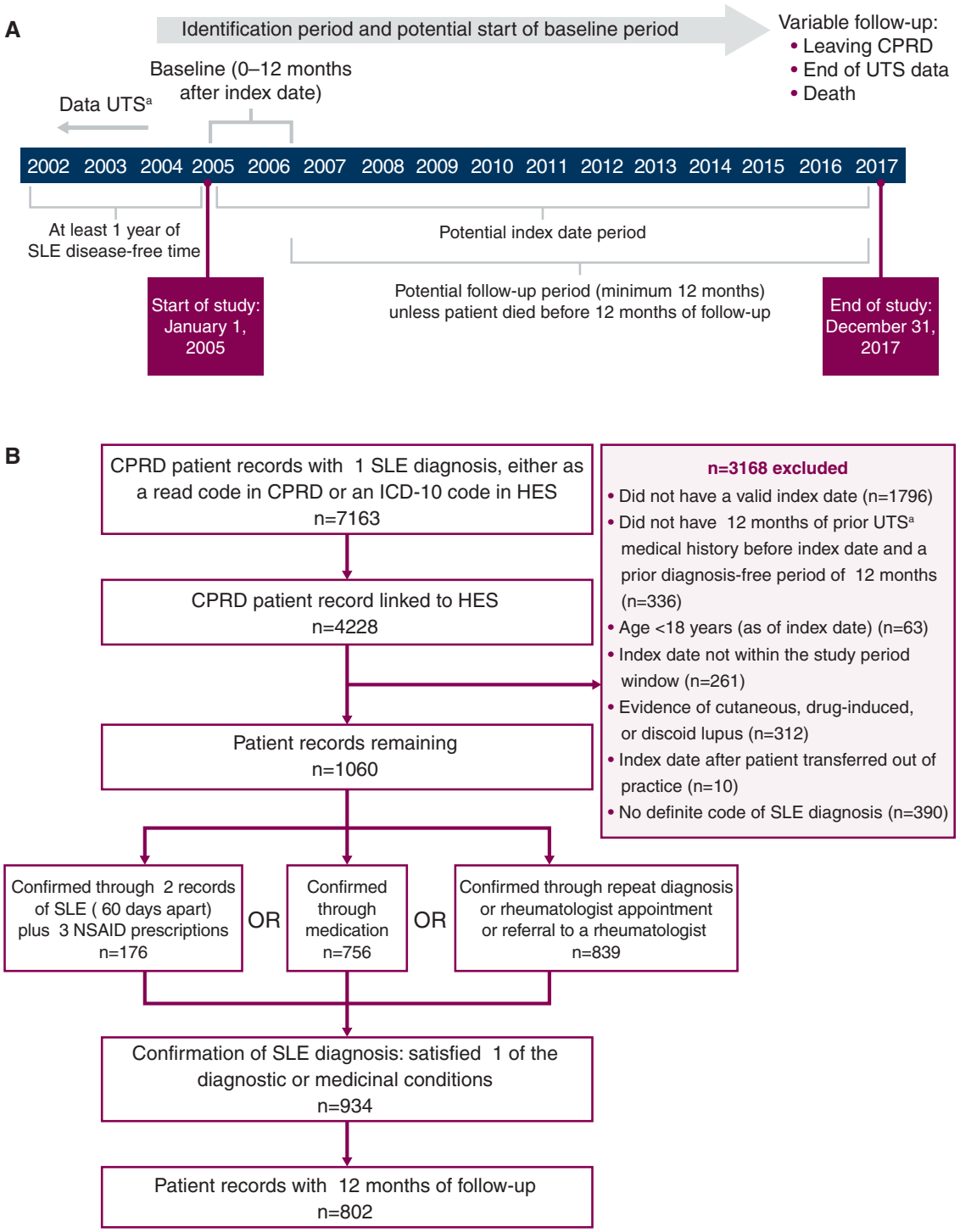
Population

All patients presenting to a general practitioner or hospital, aged ≥18 years and with at least one diagnosis of SLE during the study period were eligible for inclusion in the study. For CPRD GOLD, SLE diagnosis was recorded using a Read code, a standard clinical terminology system used in general practice in the UK, indicating a clinical test or referral event. For the HES database, SLE diagnosis was recorded using ICD-10 codes. Code lists were determined by a panel of clinical experts and aligned with published lists of SLE Read codes from previous CPRD studies [25] (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). A diagnosis of SLE was confirmed with repeat diagnosis of SLE (in CPRD or HES) or a rheumatologist appointment/referral and/or through SLE medication (Supplementary Table S2, available at *Rheumatology Advances in Practice* online) [22]. Patients were excluded if they had Read codes indicating cutaneous, drug-induced or discoid lupus rather than systemic lupus; they did not have a definite code anywhere in their CPRD record or in HES to confirm diagnosis; they transferred out of the practice before the index event date (date of first eligible diagnosis); or they did not have ≥12 months of valid data before the index diagnosis. Only new-onset (i.e. incident) cases, defined by ≥12 months of prior diagnosis-free period, were included in this analysis.

Classification of SLE disease and flare severity

Components of SLE disease measures are not captured comprehensively and routinely in real-world databases, administrative and claims data [22, 29]. SLE disease severity was classified using an algorithm that combines SLE diagnosis, SLE-related conditions (based on a

FIG. 1 Time line of study (**A**) and flowchart of study cohort (**B**)



The start of the follow-up period was immediately after the index date. The baseline period was from the index date to 12 months. Patients were followed until the earliest of these three events: end of study period; leaving the database/date of patient's last observed visit; or death. [a]UTS is the date at which the practice data are deemed of research quality. CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; ICD-10: International Classification of Diseases Tenth Revision; UTS: up-to-standard.

pre-specified list of clinical manifestations commonly associated with SLE, as outlined in the algorithm) and medications (e.g. oral CSs ≥60 mg/day as severe) [30] (Supplementary Table S3 and Fig. S1, available at *Rheumatology Advances in Practice* online) and has recently been validated for classifying patients in administrative datasets [31].

SLE disease severity was defined as mild, moderate or severe. The assigned disease severity was the highest severity experienced by a patient during a 1-year baseline period (12 months after index). SLE was categorized as severe if treatment included CYC or an oral CS (prednisone equivalent) prescription of ≥60 mg/day or diagnosis of a severe clinical manifestation (e.g. end-stage renal disease or arterial/venous thrombosis). A moderate SLE category was assigned if treatment did not include CYC or oral CSs ≥60 mg/day, if there was presence of a diagnosis of a moderate clinical manifestation (e.g. nephritis or haemolytic anaemia) or if treatment included an oral CS prescription of ≥7.5 to <60 mg/day or use of an immunosuppressive agent (excluding CYC). When patients did not meet criteria for moderate or severe disease, they were assigned as mild SLE.

SLE flares were defined using an algorithm adapted from Garris *et al.* [30] and based on the Lupus Foundation second international Lupus Flare Conference categorization [9], consensus of expert clinical opinion, and additional criteria including inpatient stays and accident and emergency (A&E) visits supported by a qualifying SLE diagnosis or SLE-related condition (Supplementary Table S3, available at *Rheumatology Advances in Practice* online).

SLE flare severity (mild, moderate or severe) was assessed by a change in treatment or initiation of a new or higher dose of treatment above a patient's regular treatment. Severe flares were identified by: (1) initiation of a prescription of CYC or oral CSs >40 mg/day or prednisone-equivalent dose; (2) inpatient admission with a primary diagnosis for SLE; or (3) inpatient admission with a primary diagnosis for an SLE-related severe clinical manifestation (Supplementary Table S3, available at *Rheumatology Advances in Practice* online). Moderate flares were identified by: (1) initiation of a prescription of oral CSs >7.5 to ≤40 mg/day prednisone-equivalent dose or immunosuppressive agent (excluding CYC); (2) an A&E admission with a primary SLE diagnosis but no inpatient admission; or (3) an A&E admission with primary or secondary diagnosis for an SLE-related moderate clinical manifestation. Mild flare included HCQ or another antimalarial; or oral CS (≤7.5 mg/day prednisone-equivalent dose); or non-immunosuppressive therapy (NSAIDs or androgens).

Measurements and outcomes

Demographics and baseline SLE-related clinical manifestations during the 12-month baseline period were summarized (Fig. 1A). SLE-related clinical manifestations were identified from a pre-specified list of conditions used for characterization of disease severity and activity (Supplementary Table S3, available at *Rheumatology Advances in Practice* online); for each condition, the proportion of patients with a record after the index date was calculated.

SLE treatment patterns, at any time during follow-up, were summarized for the following medications: oral CSs (prednisone equivalent); immunosuppressive therapy (AZA, SCA, MTX or MMF); and HCQ or other antimalarial (chloroquine phosphate or HCQ sulphate). Biologics are not captured in the CPRD database because they are administered in a specialist setting; hence, they are not included as a treatment category. We report the type of SLE medication for the total follow-up period by year, and the mean and median time to initial and subsequent treatment. We also assessed, in those patients whose first prescription was oral prednisone, either an increase in daily dose by ≥0.5 mg/kg/day or a doubling of daily dose. An increase in daily dose was defined by a new prescription of the same product started within 30 days of the end of the previous one with an increased dosage.

Statistical methods

Data were summarized using descriptive statistics, stratified by disease severity. Annualized flare rates were calculated for the total follow-up period and for each year of follow-up. We report subsequent flare rates by baseline disease severity (mild, moderate or severe).

Person-time denominators were used to account for the varying durations of individual patient follow-up. The exposure time for each prescribed treatment was assessed between the treatment start date and the first of the following events: end of study period; date of patient's last observed visit leaving the database; death; or medicinal management change (a switch from one treatment to another, an increase in dosage, an addition of another treatment or a discontinuation).

Kaplan–Meier curves were used to estimate the time to flare and hazard of flares by disease severity and the presence of clinical manifestations. We used Gray's test for equality of cumulative incidence functions [32]. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Study population

From the CPRD database, 7149 patients with an SLE Read code relating to a primary care consultation between 1 January 2005 and 31 December 2017 were identified. An additional 14 with an SLE ICD-10 code were identified in HES, yielding a total of 7163. Of the patients identified in the CPRD database, 4214 were linked to HES, of which 802 patients who had ≥12 months of prior (baseline) data and ≥12 months of follow-up where included in this analysis (Fig. 1B).

TABLE 1 Baseline characteristics and comorbidities and treatment during follow-up by severity of disease (Clinical Practice Research Datalink 2005–2017)

Parameter	All patients (*n* = 802)	Mild disease (*n* = 369)	Moderate disease (*n* = 345)	Severe disease (*n* = 88)
Patient characteristics				
Proportion female, *n* (%)	709 (88.4)	326 (88.4)	311 (90.1)	72 (81.8)
Age at index, mean (S.D.), years	48.4 (15.3)	47.1 (14.4)	48.2 (15.7)	53.9 (16.0)
Age group, *n* (%)				
18–44 years	348 (43.4)	169 (45.8)	152 (44.1)	27 (30.7)
45–64 years	321 (40.0)	149 (40.4)	134 (38.8)	38 (43.2)
≥65 years	133 (16.6)	51 (13.8)	59 (17.0)	23 (26.1)
Follow-up, years				
Mean (S.D.)	5.2 (3.0)	5.0 (3.0)	5.6 (3.0)	4.7 (2.8)
Median (25th–75th percentile)	4.9 (2.7–7.3)	4.7 (2.5–7.2)	5.4 (3.1–7.5)	4.3 (2.4–6.5)
Specific clinical manifestations[a,b], *n* (%)				
Cerebrovascular	38 (4.7)	0[c]	15 (4.3)	23 (26.1)
Moderate condition	19 (2.4)	0[c]	15 (4.3)	4 (4.5)
Severe condition	19 (2.4)	0[c]	0[c]	19 (21.6)
Hepatic and gastrointestinal	29 (3.6)	0[c]	1 (0.3)	28 (31.8)
Neurological	8 (1.0)	0[c]	4 (1.2)	4 (4.5)
Renal	58 (7.2)	0[c]	15 (4.3)	43 (48.9)
Moderate condition	27 (3.4)	0[c]	15 (4.3)	12 (13.6)
Severe condition	31 (3.9)	0[c]	0[c]	31 (35.2)
Musculoskeletal	0[c]	0[c]	0[c]	0[c]
Ocular	0[c]	0[c]	0[c]	0[c]
Other	0[c]	0[c]	0[c]	0[c]
Overall clinical manifestations, *n* (%)				
Any severe comorbidity	70 (8.7)	0[c]	0[c]	70 (79.5)
Any moderate comorbidity	52 (6.5)	0[c]	35 (10.1)	17 (19.3)
Treatment during follow-up, *n* (%)				
No treatment[d]	110 (13.7)	94 (25.0)	8 (2.3)	8 (9.1)
Oral CSs	416 (51.9)	78 (21.1)	269 (78.0)	69 (78.4)
Immunosuppressants (excluding CYC)	203 (25.3)	0[e]	175 (50.7)	28 (31.8)
Antimalarials	557 (69.5)	254 (68.8)	251 (72.8)	52 (59.1)
Biologics[f]	–	–	–	–

[a]Clinical manifestations were those included in the disease severity algorithm and were identified during the 12-month baseline period after the index date (included clinical manifestations are outlined in Supplementary Table S3, available at *Rheumatology Advances in Practice* online). [b]Categories not mutually exclusive. [c]Mild disease activity reflects clinically stable disease with no life-threatening organ involvement (i.e. no moderate or severe SLE-related comorbidities). [d]No treatment in this context means that there is no record of prescriptions for oral CSs, immunosuppressants or antimalarials; however, patients might have been treated with other medications. [e]By definition, no immunosuppressant use indicates mild disease. [f]Biologics use is not captured in the Clinical Practice Research Datalink because they are administered in a specialist care setting.

Patient characteristics and clinical manifestations in the 12-month baseline period are shown in Table 1. The mean (S.D.) age at index was 48.4 (15.3) years, and 88.4% (*n* = 709) were female. The study population was classified as: mild disease, 46.0% (*n* = 369); moderate disease, 43.0% (*n* = 345); and severe disease, 11.0% (*n* = 88) (Table 1).

During the baseline period, 70 patients (8.7%) had a severe clinical manifestation, and 52 (6.5%) had a moderate clinical manifestation (Table 1). Clinical manifestations were identified in the renal (7.2%), cerebrovascular (4.7%), hepatic and gastrointestinal (3.6%), and neurological (1.0%) organ systems. The most common clinical manifestations in the study cohort were renal failure (*n* = 28, 3.5%), gastrointestinal bleeding and ulcer (*n* = 27, 3.4%), stroke/transient ischaemic attack (*n* = 14, 1.7%), and vasculitis and aortitis (*n* = 14, 1.7%).

The mean (S.D.) follow-up duration was 5.2 (3.0) years. During the follow-up period, 43 patients (5.4%) died, of whom 11 (25.6%) had mild, 18 (41.9%) had moderate, and 14 (32.5%) had severe SLE.

Medicinal management

The majority of SLE patients (86.3%) were prescribed SLE medication, with a higher proportion in SLE patients having severe disease (90.9%) compared with those who had mild disease (75%) (Table 1). The mean (S.D.)

time to initiating any treatment (antimalarials, oral CS or immunosuppressants) after SLE diagnosis was 177 (385.3) days, and the median [interquartile range (IQR)] time to treatment was 35.5 (7–136.5) days. For antimalarials, oral CSs and immunosuppressants, the mean (S.D.) time was 133.7 (292.0), 241.4 (488.4) and 197.2 (407.7) days, respectively. Median time (IQR) was 34.0 (7–119), 41.5 (10–186), and 25 (4–124) days, respectively (Table 2; Supplementary Fig. S2, available at *Rheumatology Advances in Practice* online). A higher proportion of patients who were first prescribed immunosuppressants (78.0%) and oral CS (65.0%) subsequently went on to initiate another drug, compared with those first prescribed antimalarials (41.1%) (Table 2).

The proportion of patients prescribed oral CSs and immunosuppressants increased (from 51.9 to 57.5% and from 25.3 to 31.3%, respectively) across years 1–6 of follow-up, whereas the use of antimalarials remained stable over time (Table 3).

Of patients first prescribed oral CS ($n = 254$) at any time since the index date, 27 patients (10.6%) had an increase in daily dose of $\geq$0.5 mg/kg/day or a doubling of daily dose during the follow-up period. Furthermore, 44 (17.3%) and 97 patients (38.2%) were also prescribed NSAIDs and antimalarials, respectively, within 30 days of the end of the previous oral CS prescription.

Frequency and severity of flares

Almost all patients ($n = 750$, 93.5%) experienced at least one flare following the index date to end of follow-up (Table 4; Supplementary Fig. S3, available at *Rheumatology Advances in Practice* online). The mean (S.D.) annualized flare rate over the entire follow-up period was 3.3 (2.2). The annualized flare rates (S.D.) were 0.2 (0.6) for severe flares, 0.6 (1.3) for moderate flares, and 2.4 (2.1) for mild flares. The mean annual flare rates by severity during the first year after SLE

Table 2 Time to first prescription and follow-up treatment by type of first prescription (Clinical Practice Research Datalink 2005–2017)

Parameter	Oral CSs	Immunosuppressants[b]	Antimalarials
First prescription[a], *n* (%)			
Patients	254 (31.7)	41 (5.1)	397 (49.5)
Time to first prescription			
Mean (S.D.), days	241.4 (488.4)	197.2 (407.7)	133.7 (292.0)
Median (IQR), days	41.5 (10–186)	25.0 (4–124)	34.0 (7–119)
Subsequent treatment[a], *n* (%)			
Oral CSs only	89 (35.0)	0	0
Immunosuppressants only	0	9 (22.0)	0
Antimalarials only	0	0	234 (58.9)
Oral CSs and immunosuppressants	24 (9.4)	13 (31.7)	0
Oral CSs and antimalarials	80 (31.5)	0	86 (21.7)
Immunosuppressants and antimalarials	0	3 (7.3)	30 (7.6)
Oral CSs, immunosuppressants and antimalarials	61 (24.0)	16 (39.0)	47 (11.8)

[a]Treatment categories not mutually exclusive; a patient could have monotherapy or a combination of prescriptions as the first or subsequent prescription. [b]Excluding CYC. IQR: interquartile range.

Table 3 Prescribing trends for patients with SLE over 6 years of follow-up (Clinical Practice Research Datalink 2005–2017)

Parameter	Study duration follow-up period[a]	Years of follow-up since index date					
		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Overall, *n*	802	802	675	569	472	385	294
Proportion of patients on treatment, *n* (%)[b]							
No treatment[c]	110 (13.7)	110 (13.7)	93 (13.8)	78 (13.7)	64 (13.6)	49 (12.7)	34 (11.6)
Oral CS	416 (51.9)	416 (51.9)	361 (53.5)	307 (53.9)	257 (54.5)	215 (55.8)	169 (57.5)
Immunosuppressants[d]	203 (25.3)	203 (25.3)	180 (26.7)	155 (27.2)	135 (28.6)	118 (30.7)	92 (31.3)
Antimalarials	557 (69.5)	557 (69.5)	471 (69.8)	397 (69.8)	326 (69.1)	271 (70.4)	206 (70.1)

[a]Mean follow-up of cohort = 5.2 years. [b]Treatment groups not mutually exclusive. [c]No treatment in this context means that there is no record of prescriptions for oral CSs, immunosuppressants or antimalarials; however, patients might have been treated with other medications. [d]Excluding CYC.

TABLE 4 Annual flare rates by severity of first flare over follow-up period (Clinical Practice Research Datalink 2005–2017)

Parameter	Any flare	Mild flares	Moderate flares	Severe flares
First SLE flare, *n* (%)	750	549 (73.2)	116 (15.5)	85 (11.3)
Follow-up years, annual flare rate by severity of first flare; annual flare rate (S.D.)				
Total follow-up period[a] ($n = 802$)	3.3 (2.2)	2.4 (2.1)	0.6 (1.3)	0.2 (0.6)
Year 1 ($n = 802$)	3.5 (2.5)	2.6 (2.5)	0.7 (1.5)	0.2 (0.6)
Year 2 ($n = 675$)	3.1 (2.5)	2.4 (2.4)	0.6 (1.5)	0.1 (0.4)
Year 3 ($n = 569$)	3.2 (2.6)	2.4 (2.5)	0.7 (1.7)	0.1 (0.5)
Year 4 ($n = 472$)	3.1 (2.6)	2.3 (2.5)	0.7 (1.6)	0.1 (0.5)
Year 5 ($n = 385$)	3.0 (2.6)	2.2 (2.4)	0.7 (1.7)	0.1 (0.5)
Year 6 ($n = 294$)	3.1 (2.6)	2.3 (2.4)	0.7 (1.6)	0.1 (0.6)

[a]Mean follow-up of cohort = 5.2 years.

diagnosis are shown in Table 4. There was a trend for the annual rate to be slightly higher in year 1 than in subsequent years. For patients whose first flare was mild, subsequent flares were more likely to be mild flares; annualized flare rate (S.D.) 2.4 (2.1) compared with moderate flares 0.6 (1.3) or severe flares 0.2 (0.6). Likewise, when patients experienced an initial moderate or severe flare, the subsequent annualized flares rates were highest for moderate and severe flares, respectively.

The median time to a flare of any type was 63 days (95% CI: 57, 71). Persons with moderate and severe SLE had the shortest median time to first flare (52 days; 95% CI: 43, 65 and 61 days; 95% CI: 55, 74, respectively), followed by mild SLE (84 days; 95% CI: 64, 107; $P < 0.001$; Fig. 2A). Patients with an SLE-related clinical manifestation had a lower median time to first flare (53.5 days; 95% CI: 41, 70) compared with those without a condition (67 days; 95% CI: 57, 78; $P < 0.001$; Fig. 2B). Age and sex were not associated with the median time to first flare ($P = 0.478$ and $P = 0.745$, respectively).

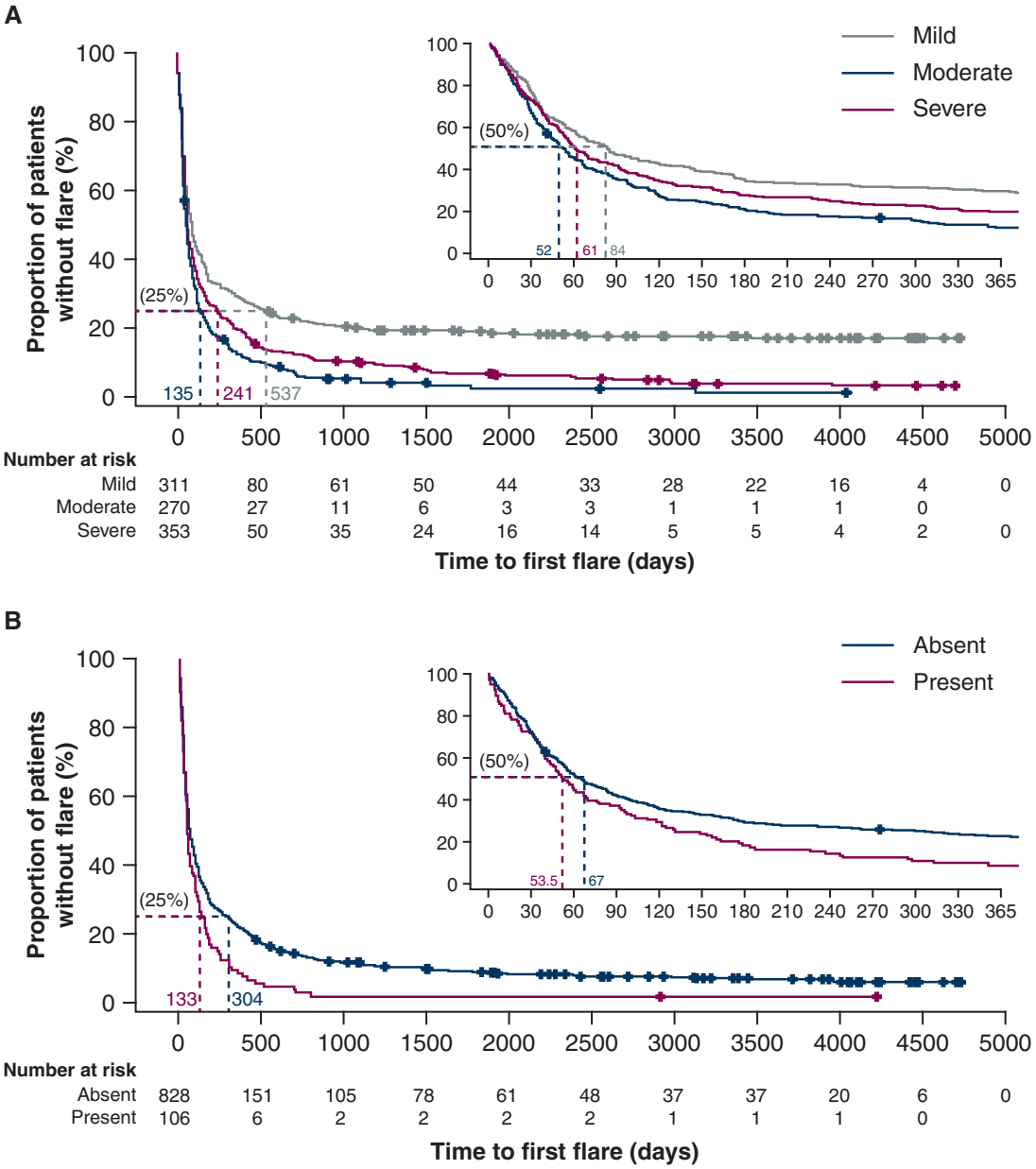
Discussion

In this longitudinal, observational cohort study characterizing newly diagnosed patients with SLE in the UK, the mean annualized flare rate identified using medical and administrative data over the whole follow-up period was 3.3 for all patients, with a median time to first flare that is significantly shorter for patients with moderate and severe disease: 52 and 61 days, respectively. We identified that moderate and severe SLE-related comorbidity affects multiple organ systems. We also determined that the presence of an SLE-related comorbidity shortened the time to first flare. Our findings suggest that it takes an average of slightly <6 months to receive treatment with antimalarial agents, oral CSs or immunosuppressive agents after an SLE diagnosis, and a consistently high proportion of patients (between 52% and 58%) continue to receive oral CSs as part of their treatment regimen over 6 years. These findings highlight potential delays in initiating treatment in newly diagnosed patients with SLE, in addition to high and sustained use of oral CSs over time. The burden of SLE flares was highest among patients with moderate and severe SLE and in patients with comorbidities, both of whom experience a shorter time to flare, at which time a large proportion of newly diagnosed patients might not have initiated treatment.

Medical management of SLE in the cohort included antimalarial agents, oral CSs and immunosuppressive agents and is generally in line with UK and European (EULAR) SLE treatment guidelines [2, 12]. The goals of treatment are to improve long-term patient outcomes and health-related quality of life; therefore, treatment regimens should be selected with the aim of remission of disease symptoms and signs, prevention of damage accrual, prevention of flares and minimization of drug side effects [12]. EULAR guidelines recommend antimalarials for all SLE patients. Our findings show that 70% of patients were prescribed antimalarials, with a mean duration of 134 days to initiate treatment after diagnosis, which is the shortest time to initiation for any of the treatments included in this analysis. EULAR guidelines also recommend the use of oral CSs for rapid symptom relief, with a medium- to long-term aim of minimizing the daily dose or to discontinue them owing to drug side effects [12]. Our study demonstrated that the use of oral CSs was high (52–58%) and remained consistently high during 6 years of follow-up. In addition, 10% of patients had an increase or doubling in the daily dose of an oral CS.

The use of medical records and claims-based algorithms to categorize SLE disease severity and flares has increased the usability of observational data to support our understanding of the real-world burden of SLE. In the present study, 54% of patients were categorized as having moderate or severe SLE at baseline, and 11.0% were categorized has having severe disease. A previous observational study from the USA, which also used a claims-based algorithm, identified a higher proportion of patients with moderate and severe disease

FIG. 2 Time to first flare by SLE severity (**A**) and clinical manifestations (Clinical Practice Research Datalink 2005–2017) (**B**)



Dashed lines in the main plot show the 25th percentile. Dashed lines in the inset show the 50th percentile (median). Corresponding values (days) are given. (A) This analysis was conducted on the cohort of patients with any length of follow-up and not restricted to those with ≥12 months of follow-up (n=934). (B) The presence of a clinical manifestation was based on the cohort with ≥12 months of follow-up (n=802). Clinical manifestations were adjusted for age, sex, SLE severity and comorbidities.

(moderate, 52.1% and severe, 21.5%) [30]. The lower proportion of severe disease identified in the present study might be attributable, in part, to the unavailability of data on biologic agents within the CPRD and HES data. Biologics, such as belimumab or off-label rituximab, are recommended by guidelines for use only in patients with more severe disease and inadequate control or refractory to other agents [12]. Claims-based studies, which use medical records and administrative data when available, might have utility in categorizing SLE disease severity when clinical characterization is not available [31]. The algorithms used in the present study involve classification by prescription data and clinical manifestations with linkage to hospital and mortality

records, which is an enhancement of previous classification systems that use only prescription data [22]. Our study identified flares in 93.5% of the cohort and an overall mean annual flare rate per patient of 3.3. This is comparable to the observational study conducted in the USA, in whic 95.7% of the cohort experienced flares, and the mean number of flares per patient over 2 years was 6.7 [30].

The use of individual patient-level data extracted from a large nationwide general practice records database and linked to hospital and mortality records is one of the strengths of this study. Our study cohort is representative of the UK general population, which makes our findings generalizable to patients in the UK with SLE treated in primary care. The ability to follow patients over 6 years improves real-world understanding of longitudinal trends in SLE disease characteristics and treatment. The CPRD has been used for a number of SLE-related studies, mostly to assess the incidence of SLE in the UK [17–28]. The most recent CPRD study used a case-identification algorithm; however, no linkage to HES or categorization of disease activity was made, and categorization of disease severity was done using prescription records only [22].

The limitations of our study are common to retrospective observational studies using routinely collected electronic health record data. First, CPRD GOLD linkage data are available for only 50% of contributing CPRD GOLD practices in the UK. In addition, these data may include missing data and potential biases, such as misclassification biases, or inconsistencies in coding within and between practices and over time. To reduce potential misclassification in our study, we required linkage with HES and $\geq$12 months of follow-up and, in addition, we required confirmation of SLE diagnosis through repeat diagnosis of SLE (in CPRD or HES), through a rheumatologist appointment or referral, or through SLE medication use. This might represent an underestimation of the true number of SLE cases and an overestimation of patients with more severe disease. However, only 1.8% ($n = 126$) of patients were excluded owing to a lack of additional verifying information. This indicates that the potential bias created by requiring confirmation of SLE diagnosis is small. Second, drugs prescribed in the specialist setting, such as biologics, are not available routinely in the CPRD and are therefore not included in this study.

Furthermore, the use of electronic health records to assign severity of disease and flares can be challenging, because SLE is a clinically complex disease, and disease severity and activity measures, such as the SLEDAI-2K, are not captured routinely in real-world databases or administrative and claims data [22, 29, 33]. However, we adapted algorithms developed for a study from the USA that used information about prescriptions and clinical manifestations to determine both disease severity and flare severity. The algorithms were developed from existing validated tools and clinical opinion [30] and have recently undergone validation against the SLEDAI-2K and been shown to have acceptable performance for classification of SLE severity [31]. Although further validation of these algorithms, which serve as a proxy for SLE disease and flare severity, is warranted, the use of real-world evidence to understand SLE would be vastly improved if validated measures of disease severity and flares were routinely captured in electronic health record and claims data for use in future observational research.

This study provides a detailed picture of SLE disease severity and flares over time in patients in the UK, together with an overview of current medical management patterns and the types of comorbidities present. Our findings suggest potential delays in SLE treatment initiation in the UK. Early treatment might delay or reduce the severity of the first SLE flare after diagnosis and might translate to slower disease progression, lower organ damage accrual, better outcomes and improved health-related quality of life.

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Data availability statement

This study is based in part on data from CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. The Office for National Statistics provided the mortality data. The interpretation and conclusions contained in this study are those of the authors alone. The authors do not own these data and hence are not permitted to share the data in the original form.

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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