Treatment of systemic lupus erythematosus: analysis of treatment patterns in adult and paediatric patients across four European countries

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Abstract

Objective
Multiple treatment options are recommended for Systemic Lupus Erythematosus (SLE) by clinical guidelines. This study aimed to explore SLE treatment patterns as there is limited real-world data of SLE medication utilisation, especially in childhood-onset SLE (cSLE).

Methods
We conducted a longitudinal cohort study using five routinely collected healthcare databases from four European countries (United Kingdom, France, Germany, and Spain). We described the characteristics of adult and paediatric patients at time of SLE diagnosis. We calculated the percentage of patients commencing SLE treatments in the first month and year after diagnosis, reported number of prescriptions, starting dose, cumulative dose, and duration of each treatment, and characterised the line of therapy.

Results
We characterised 11,255 patients with a first diagnosis of SLE and included 5,718 in our medication utilisation analyses. The majority of adult SLE patients were female (range 80-88%), with median age of 49 to 54 years at diagnosis. In the paediatric cohort (n=378), 66-83% of SLE patients were female, with median age of 12 to 16 years at diagnosis. Hydroxychloroquine and glucocorticoids were common first-line treatments in both adults and children, with second-line treatments including mycophenolate mofetil and methotrexate. Few cases of monoclonal antibody use were seen in either cohort. Initial glucocorticoid dosing in paediatric patients was often higher than in adults.

Conclusion
Treatment choices for adult SLE patients across four European countries were in line with recent therapeutic consensus guidelines. High glucocorticoid prescriptions in paediatric patients suggests the need for steroid-sparing treatment alternatives and paediatric specific guidelines.

Funding
Daniel Prieto-Alhambra (DPA) receives funding from the UK National Institute for Health and Care Research (NIHR) in the form of a senior research fellowship. DPA's group received partial support from the Oxford NIHR Biomedical Research Centre. This study was funded by the European Medicines Agency as part of the DARWIN EU® project(EMA/2021/08/TDA).

Research in context

Evidence before this study
On November 30th 2023, we searched PubMed for articles published in English since January 1st 2013 using the keywords (systemic lupus erythem*) AND ((treatment pattern*) OR ((medication OR drug) AND (use OR utilisation))) with no restrictions on study type. We identified 17 studies investigating treatment patterns in adult SLE patients in North America, Europe, Asia and Australia, however, significant heterogeneity existed in their study designs, data sources, and outcome measures. Very few studies reported medication dose or treatment length, and if reported these were limited to glucocorticoids. The only paediatric drug utilisation data found were from the United Kingdom and United States.

Added value of this study

This is the first study to concurrently collect data on medicine utilisation in SLE from five separate databases from four European countries, allowing comparison between countries, and mitigating the risk of drawing conclusions from just one dataset. We report medicine utilisation patterns in adults with SLE but also in c-SLE where data are particularly scarce globally. Where data are available, we report treatment duration, average and cumulative dose, and number of prescriptions for each potential SLE treatment.

Implications of all the available evidence

We confirm that first-line treatment for SLE in both adult and paediatric patients is predominantly glucocorticoids and hydroxychloroquine, as recommended by European guidelines. Second-line medications most frequently include mycophenolate mofetil and methotrexate. The use of monoclonal antibodies such as belimumab was seen relatively rarely, and future studies may seek data on other more recently licensed monoclonals. Glucocorticoid use is significant in SLE and is particularly pronounced in cSLE. Due to the effects of growth and development, children and adolescents can be at risk of long-term adverse effects from these medications. This study provides important stimulus for further development of novel approaches in cSLE and supports efforts to refine standards in clinical care based on more detailed treatment recommendations. In addition, ongoing and future exploration of medicine utilisation patterns will help guide the regulatory review of evidence and resulting drug labelling and monitor the impact of changing treatment guidelines in adult and paediatric SLE.

Background

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder of connective tissue with a highly variable clinical presentation, disease course and prognosis (1). SLE is characterised by periods of remission and flares, and the presence of autoantibodies that target nuclear antigens (2). The disease is thought to be more severe in childhood-onset SLE (cSLE), with higher prevalence of morbidity and lower survival rates (3).

Various treatment options exist for SLE. The 2019 and 2023 European Alliance of Associations for Rheumatology (EULAR) treatment guidelines do not differentiate between adults and children and recommend hydroxychloroquine as first-line treatment (4, 5). Glucocorticoids provide rapid symptomatic relief, but long-term safety concerns limit their use. They are recommended as 'bridging treatment' for disease flares but only to be used at low doses in the longer term and withdrawn completely where possible (5). The guidelines also recommend the addition of disease-modifying antirheumatic drugs (DMARD) or immunosuppressants to control flares and facilitate glucocorticoid tapering (4, 5). Examples of DMARDs used in SLE include methotrexate, azathioprine, mycophenolate mofetil, and cyclophosphamide.

Biological agents such as belimumab should be considered in extrarenal disease, and anifrolumab as an add-on therapy in moderate to severe active disease, while rituximab might be used off-label in patients with refractory or severe disease (4, 6). Calcineurin inhibitors are recommended as monotherapy or in combination with mycophenolate mofetil in patients at high risk of renal involvement (4).

In contrast to adult SLE, there is limited good quality evidence on the treatment of cSLE. A European-wide panel of paediatric rheumatologists recommended routine treatment using hydroxychloroquine (7) with the addition of DMARDs if disease cannot be adequately controlled. Rituximab was used in a limited number of cases (7). Moreover, only few medicines used in cSLE have a specific indication covering paediatric patients (hydroxychloroquine, methylprednisolone, azathioprine). Belimumab was authorised by the EMA in 2019 as the first monoclonal antibody therapy for the treatment of patients aged 5 years and older with SLE. However, evidence around medications used in practice in cSLE is lacking.

Understanding treatment patterns of drugs used in complex diseases such as SLE is important for multiple reasons. It allows assessment of the burden of treatments, which often carry risks of serious adverse effects, and is especially important in the paediatric population where data are scant. Furthermore, such data can provide evidence to guide drug development in designing clinical trials, regulatory drug labelling, guideline development, and healthcare resource planning.

In this study we aim to characterise adult and paediatric patients diagnosed with SLE between 2013-2022, using data from four European countries: the United Kingdom (UK), Germany, France, and Spain. We also seek to describe the medication types, treatment patterns, and dosing of treatments used in these SLE populations.

Methods

Study design

A longitudinal cohort study of all people newly diagnosed with SLE was conducted. The study protocol was registered in the EUPAS Registry (EUPAS106436).

Settings and data sources

The study was conducted using routinely collected health data from five databases, which were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). These were:

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Institut Municipal Assistència Sanitària Hospital del Mar Information System (IMASIS), Spain
4. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
5. Clinical Practice Research Datalink (CPRD) GOLD, UK

Three of these are primary care databases including information from general practitioners (GPs) and specialists (IQVIA DA Germany, CPRD and SIDIAP) and two are hospital databases (IMASIS and CDWBordeaux). Only outpatient therapies were captured in the primary care datasets. Complete hospital-based SLE treatment data were available in IMASIS and CDWBordeaux. A proportion of the SIDIAP database had linkage to hospital discharge data to allow for more accurate patient characterisation in terms of diagnoses, but data on inpatient treatments were not available. As there were no paediatric patients in IMASIS, this database was not used for paediatric analyses. Further information on the data sources are described in Supplementary Table S1.

The study period was from 01/01/2013 until the latest observation date in each database. The patient selection period was from 01/01/2013 to 180 days prior to the latest observation period end date in each of the data sources (Supplementary Table S2).

Participants

The study population included all individuals with a first diagnosis of SLE identified in the database during the patient selection period. Patients were selected based on the occurrence in their medical records of Systematized Nomenclature of Medicine (SNOMED) diagnostic codes. A systematic search to identify possible codes for inclusion was performed using the CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). Potential codes were reviewed by two clinical epidemiologists. A final list of included codes is provided in Supplementary Table S3.

Participants were included in 'new diagnosis' cohorts if they had a first diagnosis of SLE in a database during the patient selection period, had at least 365 days of prior history available at first SLE diagnosis date, and were aged either ≥18 (adult cohort) or <18 (paediatric cohort).

Participants were included in 'new user' cohorts if they met the inclusion criteria for the cohorts above, and additionally initiated an SLE treatment of interest after the first diagnosis of SLE, with no record of that specific treatment in the year before initiating the treatment.

Variables

Exposures

Exposure to the following pre-defined SLE treatments were measured: hydroxychloroquine, systemic glucocorticoids, methotrexate, azathioprine, calcineurin inhibitors (tacrolimus, cyclosporine,

voclosporin), mycophenolate, cyclophosphamide, rituximab, and belimumab (Supplementary Table S4). When defining drug cohorts, non-systemic products were excluded from the list of included codes summarised on the ingredient level. A pharmacist reviewed the codes for the SLE treatments.

Other covariates

The following covariates were measured: Age at SLE diagnosis; sex; all co-morbidities and co-medications recorded at defined time points prior to and at index date were used for large-scale patient characterisation (Supplementary Table S5). Additionally, a list of pre-specified co-morbidities and co-medications relevant for patients with SLE was described (Supplementary Table S6).

Study size

No sample size was calculated as this is a descriptive study with the objective of characterising all available incident SLE patients. Prior to developing the study protocol, feasibility counts were generated for this study in the respective databases.

Statistical methods

For all continuous variables, median with interquartile ranges were reported. For all categorical analyses, number and percentages were reported.

We used R packages for the patient-level characterization of demographics and clinical characteristics; "DrugUtilisation" (https://github.com/darwin-eu/DrugUtilisation) for the drug utilisation analyses; "TreatmentPatterns" (https://github.com/darwin-eu-dev/TreatmentPatterns) for the characterisation of treatments including combination and sequence of therapy. These packages include numerous automated unit tests to ensure the validity of the codes, alongside reviewed and user tested software.

The analytical code for the study is available via https://github.com/darwin-eu-studies/P2-C1-006-SLE-study/

Patient-level characterisation

Age and sex at time of first SLE diagnosis (index date) were described. Comorbidities and concomitant medication use were reported as a proportion at pre-defined time points (Supplementary Table S5).

Patient-level drug utilisation

The number and percentage of patients receiving each of a pre-defined SLE treatments and treatment combinations were described per calendar year. Sunburst plots and Sankey diagrams (censored at the end of treatment/follow-up) were used to visualise treatment patterns and sequences over time.

For the new user cohort, the index date is the initiation of each SLE treatment after SLE diagnosis. Treatment duration, initial dose/strength, cumulative dose, number of prescriptions were estimated for new users of SLE treatments at the ingredient level.

Drug exposure calculations

Drug eras were defined as follows: Exposure to a drug started at the date of the first prescription after the first SLE diagnosis. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM. Subsequent prescriptions for the same drug were combined

into continuous exposed episodes (drug eras) if the gap was ≤ 30 days (Supplementary Figure S1). For dose calculation, the overlap time between two prescriptions was considered as the dose of the first exposure (Supplementary Figure S2). No time was added at the end of the combined drug era to account for the overlap. We did not consider re-exposure after treatment discontinuation.

A number of parameters were defined in the TreatmentPatterns package (8) to construct treatment pathways (Supplementary Figure S3, Supplementary Table S7).

A minimum cell count of 5 was used when reporting results per database with any smaller counts reported as "<5". All analyses were reported by country/database, overall and stratified by age and sex where possible (minimum cell count reached). Sunburst plots, Sankey diagrams were further stratified by study periods (2013-2017 and 2018-2022).

Missing values

We assumed that the absence of prescription records meant that the person did not receive the respective drug. We reported the missingness of dose information for each treatment ingredient in each database, but no imputation was performed on the missing values.

Role of the funding source

This study was funded by EMA and performed via DARWIN EU®. The study funder was involved in reviewing the protocol and the objectives, reviewing the results report and contributing to the manuscript.

Results

All results are available in a web application ("Shiny app") at https://dpa-pde-oxford.shinyapps.io/P2-C1-006SLE/

Baseline characteristics

We identified 11,255 patients with a first diagnosis of SLE (new diagnosis cohort) across the study databases (Table 1). From these, we included 5,718 patients who started treatment for SLE at or after diagnosis, without prior use at the treatment ingredient level in the 365 days prior to index date, in the drug utilisation study (new user cohort) (Table 1).

Table 1. Attrition table showing the number of participants initially eligible, and finally included in each cohort, following attrition.

	Number of patients per database				
Reason	**CDWBordeaux**	**CPRD GOLD**	**IMASIS**	**IQVIA Germany DA**	**SIDIAP**
First diagnosis of SLE	1506	7528	821	12497	11464
Index date within the study period	987	2030	390	7880	6315
At least 365 days of prior observation **(new diagnosis cohort)**	697	1555	295	2744	5964
Limited to new user of SLE treatments **(new user cohort)**	408	1027	209	1016	3058

Of 11,255 patients with SLE, 378 were aged <18 years, the majority were female (range 66-83%), with median age at first diagnosis ranging from 12 to 16 years (Table 2). In general, paediatric patients had few recorded comorbidities before SLE diagnosis. The most common comorbidities were asthma (6-15%), pneumonia (10-13%), anxiety (8-13%), and other autoimmune diseases (3-16%). The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (35-38%), systemic antibacterial drugs (25-45%), and drugs for acid-related disorders (6-21%).

Table 2. Baseline patient characteristics stratified by database for paediatric SLE participants

Variable	CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
N	13	42	68	255
Female	10 (77%)	35 (83%)	52 (76%)	169 (66%)
Age median [min; q25 - q75; max]	16 [6; 14 - 16; 17]	15 [2; 12 - 16; 17]	14 [2; 10 - 16; 17]	12 [1; 8 - 15; 17]
Age group				
0 to 4	<5	<5	7 (10%)	23 (9%)
5 to 12	<5	9 (21%)	19 (28%)	111 (44%)
13 to 17	11 (85%)	30 (71%)	42 (62%)	121 (47%)
Comorbidities (any time prior)				
Anxiety	0 (0%)	<5	9 (13%)	21 (8%)
Asthma	0 (0%)	5 (12%)	10 (15%)	15 (6%)
Other autoimmune disease	0 (0%)	<5	11 (16%)	8 (3%)
Pneumonia	0 (0%)	<5	7 (10%)	32 (13%)
Comedications (prior year)				
Antibacterials (systemic)	0 (0%)	19 (45%)	22 (32%)	64 (25%)
Anti-inflammatory/ antirheumatic products	<5	16 (38%)	24 (35%)	98 (38%)
Drugs for acid related disorder	<5	9 (21%)	6 (9%)	16 (6%)
Drugs for obstructive airway disorder	0 (0%)	5 (12%)	<5 (NA%)	28 (11%)

There were 10,879 patients in our adult new diagnosis cohort, 80-88% were female, with median age of 49 to 54 years (Table 3). The most common comorbidities in the adult population were other autoimmune diseases (9-35%), hypertension (15-27%), and anxiety (6-27%) across all databases. The most common medications prescribed in the year before SLE diagnosis were anti-inflammatory/anti-rheumatic products (12-57%), systemic antibacterials (8-53%), and drugs for acid-related disorders (11-51%).

Table 3. Baseline patient characteristics stratified by database (adult SLE).

Variable	CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
N	684	1,513	295	2,676	5,709
Female	573 (84%)	1,331 (88%)	243 (82%)	2,218 (83%)	4,562 (80%)
Age median [min; q25 - q75; max]	49 [18; 36 - 61; 93]	49 [18; 38 - 61; 95]	54 [18; 44 - 67; 94]	54 [18; 43 - 65; 94]	50 [18; 39 - 64; 101]
Age group					
18 to 39	217 (32%)	443 (29%)	58 (20%)	554 (21%)	1,542 (27%)
40 to 49	128 (19%)	345 (23%)	49 (17%)	481 (18%)	1,247 (22%)
50 to 59	150 (22%)	305 (20%)	72 (24%)	676 (25%)	1,138 (20%)
60 to 69	98 (14%)	219 (14%)	53 (18%)	504 (19%)	796 (14%)
70 to 150	91 (13%)	201 (13%)	63 (21%)	461 (17%)	986 (17%)
Comorbidities (any time prior)					
Anxiety	42 (6%)	344 (23%)	27 (9%)	331 (12%)	1,557 (27%)
Asthma	19 (3%)	198 (13%)	7 (2%)	206 (8%)	309 (5%)
Other autoimmune disease	95 (14%)	320 (21%)	26 (9%)	936 (35%)	956 (17%)
Chronic kidney disease	30 (4%)	128 (8%)	14 (5%)	190 (7%)	399 (7%)
Chronic liver disease	6 (1%)	14 (1%)	9 (3%)	31 (1%)	92 (2%)
COPD	25 (4%)	47 (3%)	31 (11%)	190 (7%)	232 (4%)
Dementia	<5	<5	<5	25 (1%)	80 (1%)
Depressive disorder	11 (2%)	347 (23%)	32 (11%)	482 (18%)	858 (15%)
Diabetes mellitus	36 (5%)	70 (5%)	20 (7%)	240 (9%)	437 (8%)
Gastroesophageal reflux disease	22 (3%)	60 (4%)	<5	123 (5%)	335 (6%)
Heart failure	20 (3%)	17 (1%)	20 (7%)	125 (5%)	196 (3%)
Hypertension	106 (15%)	223 (15%)	59 (20%)	717 (27%)	1,359 (24%)
Hypothyroidism	33 (5%)	153	12 (4%)	240 (9%)	692

		(10%)			(12%)

Inflammatory bowel disease	6 (1%)	21 (1%)	<5	53 (2%)	63 (1%)
Malignant neoplastic disease	35 (5%)	69 (5%)	30 (10%)	200 (7%)	475 (8%)
Myocardial infarction	5 (1%)	21 (1%)	<5	29 (1%)	83 (1%)
Osteoporosis	25 (4%)	67 (4%)	11 (4%)	238 (9%)	426 (7%)
Pneumonia	20 (3%)	53 (4%)	32 (11%)	133 (5%)	432 (8%)
Rheumatoid arthritis	25 (4%)	71 (5%)	8 (3%)	421 (16%)	184 (3%)
Stroke	14 (2%)	29 (2%)	5 (2%)	71 (3%)	158 (3%)
Venous thromboembolism	26 (4%)	93 (6%)	9 (3%)	150 (6%)	179 (3%)
Comedications (prior year)					
Agents acting on RAAS	22 (3%)	286 (19%)	21 (7%)	387 (14%)	1,201 (21%)
Antibacterials (systemic)	52 (8%)	798 (53%)	54 (18%)	399 (15%)	2,054 (36%)
Antidepressants	16 (2%)	534 (35%)	29 (10%)	170 (6%)	1,297 (23%)
Antiepileptics	22 (3%)	208 (14%)	28 (9%)	75 (3%)	677 (12%)
Anti-inflammatory/ antirheumatic products	82 (12%)	791 (52%)	116 (39%)	768 (29%)	3,230 (57%)
Antineoplastic agents	21 (3%)	104 (7%)	9 (3%)	104 (4%)	225 (4%)
Antithrombotics	55 (8%)	196 (13%)	41 (14%)	169 (6%)	612 (11%)
Beta blocking agents	18 (3%)	211 (14%)	12 (4%)	291 (11%)	510 (9%)
Calcium channel blockers	28 (4%)	215 (14%)	15 (5%)	152 (6%)	520 (9%)
Diuretics	24 (4%)	206 (14%)	25 (8%)	171 (6%)	624 (11%)
Drugs for acid related disorder	76 (11%)	768 (51%)	75 (25%)	486 (18%)	2,443 (43%)
Drugs for obstructive airway disorder	21 (3%)	425 (28%)	37 (13%)	167 (6%)	1,121 (20%)
Drugs used in diabetes	17 (2%)	68 (4%)	19 (6%)	93 (3%)	362 (6%)

Hormonal contraceptives	0 (0%)	164 (11%)	<5 (NA %)	29 (1%)	133 (2%)
Immunosuppressants	29 (4%)	172 (11%)	29 (10%)	230 (9%)	416 (7%)
Lipid modifying agents	23 (3%)	257 (17%)	12 (4%)	196 (7%)	1,011 (18%)
Opioids	45 (7%)	613 (41%)	37 (13%)	174 (7%)	1,049 (18%)
Psycholeptics*	58 (8%)	307 (20%)	57 (19%)	124 (5%)	1,952 (34%)

COPD: Chronic Obstructive Pulmonary Disease, GERD: Gastroesophageal Reflux Disease, RAAS: Renin Aldosterone Angiotensin System. *Psycholeptics refer to the WHO-ATC N05 group, which includes antipsychotics, anxiolytics, hypnotics, and sedatives.

Treatment patterns of SLE patients (new diagnosis cohort)

Among the paediatric SLE cohort, the most frequent treatments within the first 30 days after diagnosis were glucocorticoids (10-54%) and hydroxychloroquine (14-46%) (Figure 1, Supplementary Table S8) across CDWBordeaux, CPRD GOLD, and SIDIAP. In IQVIA Germany DA, there were fewer than 5 patients treated with the pre-specified treatments.

The most frequent treatments within the first year of diagnosis were hydroxychloroquine (9-62%), glucocorticoids (12-62%), and mycophenolate mofetil (5-46%) across all databases (Figure 2, Supplementary Table S9). The use of rituximab (38%, n=5) was observed in the hospital setting (CDWBordeaux) only.

Use of azathioprine (4%), tacrolimus (4%), and methotrexate (2%) were also observed albeit rarely in SIDIAP.

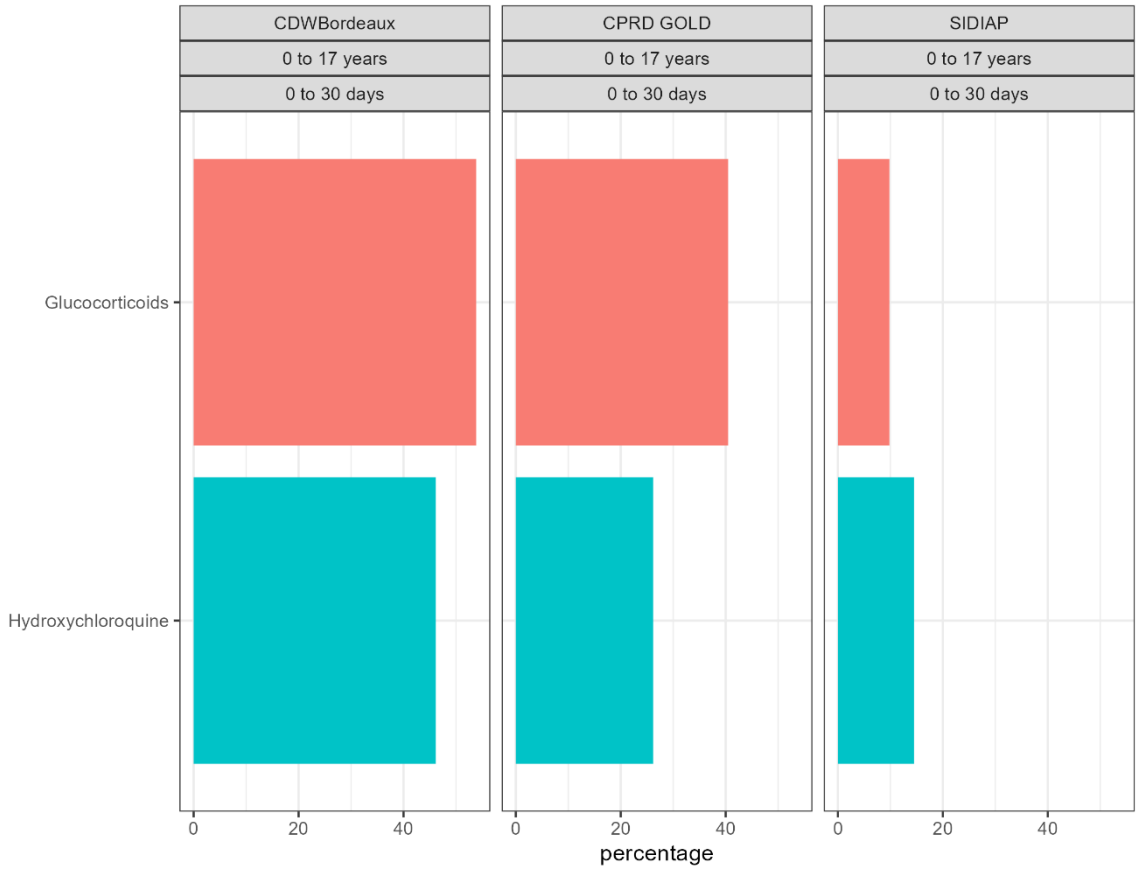

Figure 1. New users of SLE treatment within 30 days following diagnosis, stratified by database (paediatric cohort)

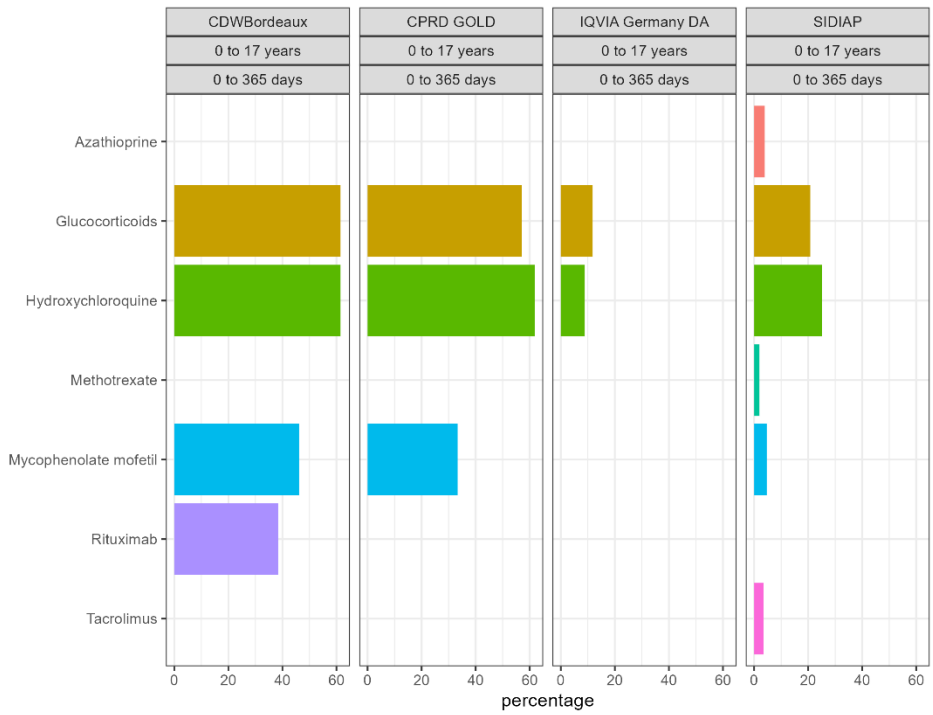

Figure 2. New users of SLE treatment within 365 days following diagnosis, stratified by database (paediatric cohort)

In the adult cohort, the most frequent treatments within the first 30 days of diagnosis were hydroxychloroquine (8-32%) and glucocorticoids (11-33%) (Figure 3, Supplementary Table S8). The most frequent used treatments within the first year of diagnosis were hydroxychloroquine (13-49%), glucocorticoids (18-42%). The third most frequently used treatment was mycophenolate mofetil (6%) in CDWBordeaux and methotrexate (4-7%) in all other databases (Figure 4, Supplementary Table S9).

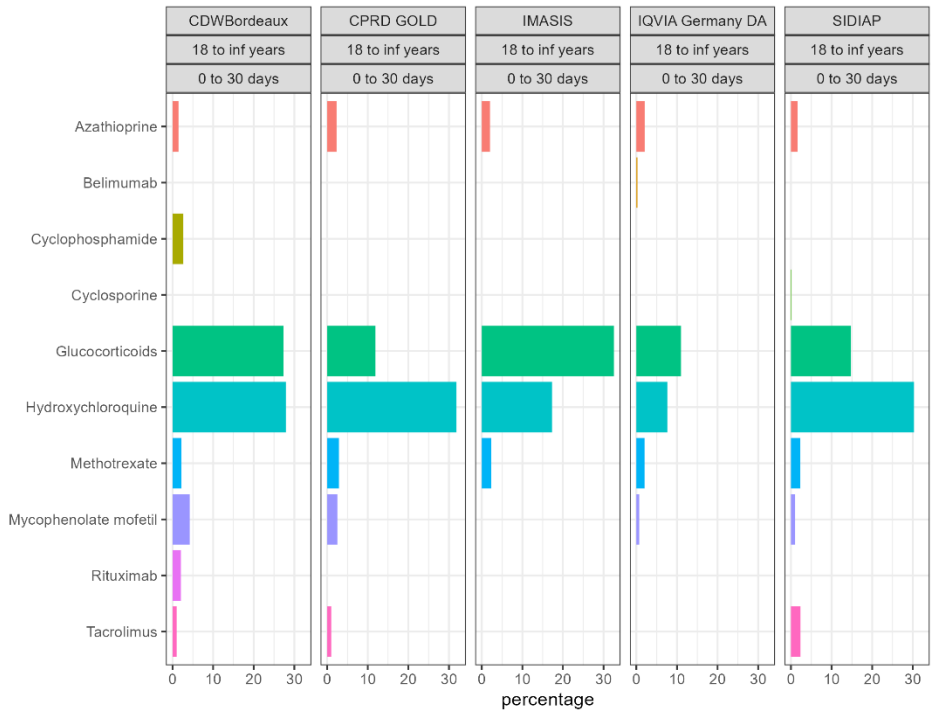

Figure 3. New users of SLE treatment within 30 days of diagnosis, stratified by database (adult cohort)

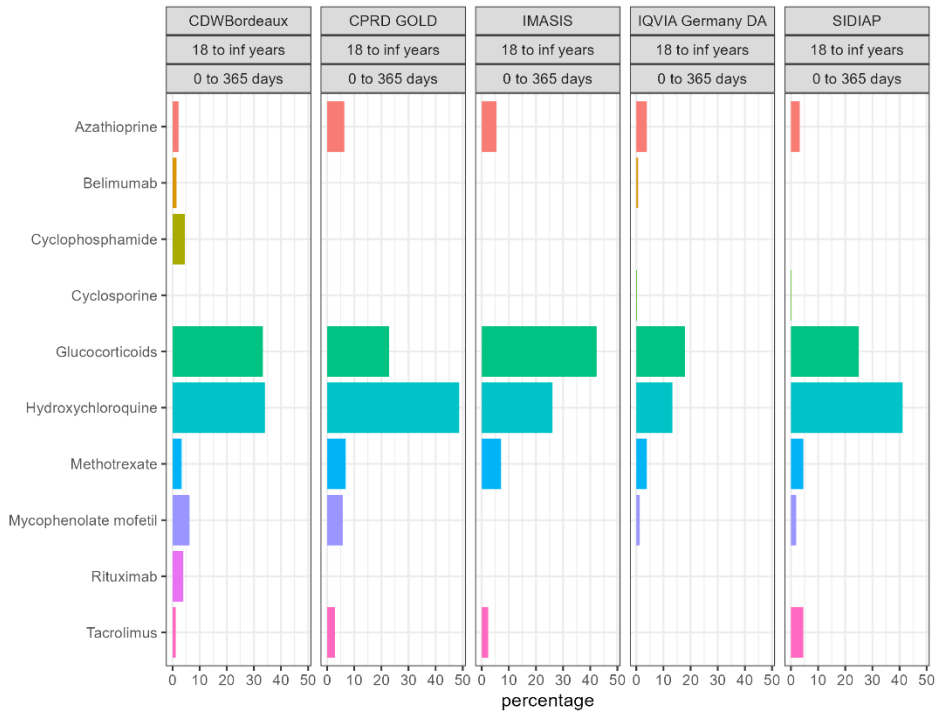

Figure 4. New users of SLE treatment within 365 days of diagnosis, stratified by database (adult cohort)

Sunburst plots were computed for the overall cohort for each database, as small numbers in the paediatric cohort meant that treatment pathways were obscured due to privacy rules (Supplementary Figure S4). In CPRD GOLD and SIDIAP, hydroxychloroquine was the most frequent first treatment identified after diagnosis. (Supplementary Figures S4A and S4B). Of these patients, in CPRD GOLD, the second-line treatment was monotherapy/addition of glucocorticoids or methotrexate, monotherapy of mycophenolate mofetil. In SIDIAP, the second-line treatment consisted of glucocorticoids, tacrolimus, and azathioprine. In IQVIA DA Germany (Supplementary Figure S4C), glucocorticoids were most frequently used as first-line treatment, the second-line treatment consisted of azathioprine, hydroxychloroquine, and methotrexate. Sankey diagrams showing the switches between different SLE treatments are represented in the overall cohort for each database in Supplementary Figures 5-7.
No plots were generated for CDWBordeaux and IMASIS as these hospital databases did not have sufficient information on treatment episode duration to allow the study of treatment sequences.

Drug utilisation analysis of SLE treatments (new user cohort)

The treatment duration, number of prescriptions, initial and cumulative dose were calculated for each of the treatments of interest, in the paediatric (Table 4) and adult (Table 5) cohorts. Dose information was not available for CDWBordeaux.

In the paediatric new user cohort, the most frequently used SLE treatments are hydroxychloroquine, followed by prednisone/prednisolone. For hydroxychloroquine, median duration was between 50 to 501 days for primary care databases and 8 days for CDWBordeaux hospital, median initial daily dose ranged from 199 to 300 mg, median cumulative dose ranged from 20,000 to 116,600 mg, number of prescriptions in the first drug era was 1 to 10 across all databases. For prednisone/prednisolone, median duration ranged between 74 to 246 days in primary care databases, 13 days in hospital; median initial daily dose ranged from 10 to 60 mg, cumulative dose ranged from 775 to 2,150 mg, number of prescriptions was 1 to 5 across all databases.

In the adult new user cohort, the most frequently used SLE treatment was hydroxychloroquine, followed by prednisone/prednisolone. For hydroxychloroquine, median duration was 39 to 485 days for primary care databases and 4 to 30 days for hospital databases, median initial daily dose ranged from 13 to 400 mg, median cumulative dose ranged from 600 to 130,051 mg, number of prescriptions in the first drug era was 1 to 6 across all databases. For prednisone/prednisolone, median duration was 7 to 111 days for primary care databases and 4 to 30 days for hospital databases; across all databases, median initial daily dose (2 to 40 mg), cumulative dose (20 to 1,038 mg), with 1 to 4 prescriptions. The results for the other SLE treatments with counts in at least 2 databases are summarised in Table 5. The results for the other treatments are available in the Shiny app.

Table 4. Drug utilisation of SLE treatments in paediatric cohort

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
0 to 17	Hydroxychloroquine	**Number of subjects**				
		count (n)	8	23	8	58
		Duration, days				
		Median (IQR)	8 [4 - 14]	110 [50 - 323]	50 [45 - 94]	501 [252 - 1,808]
		Number of prescriptions				
		Median (IQR)	10 [4 - 11]	4 [2 - 8]	1 [1 - 1]	3 [1 - 6]
		Initial daily dose, mg				
		Median (IQR)	NA	200 [200 - 200]	300 [200 - 400]	199 [197 - 199]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)
		Cumulative daily dose, mg				
		Median (IQR)	NA	24,000 [11,200 - 69,800]	20,000 [16,500 - 21,500]	116,600 [52,250 - 446,043]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)
0 to 17	Mycophenolate mofetil	**Number of subjects**				
		count (n)	7	16	5	14
		Duration, days				
		Median (IQR)	4 [2 - 15]	371 [114 - 796]	75 [44 - 80]	216 [104 -

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
						344]
		Number of prescriptions				
		Median (IQR)	4 [2 - 15]	12 [6 - 27]	2 [1 - 2]	3 [1 - 5]
		Initial daily dose, mg				
		Median (IQR)	NA	893 [562 - 2,000]	1,974 [1,500 - 1,974]	992 [959 - 1,053]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)
		Cumulative daily dose, mg				
		Median (IQR)	NA	621,000 [212,500 - 1,627,750]	150,000 [75,000 - 150,000]	338,896 [133,312 - 767,522]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)
0 to 17	Prednisone/ Prednisolone*	**Number of subjects**				
		count (n)	6	21	8	47
		Duration, days				
		Median (IQR)	13 [1 - 25]	74 [17 - 157]	75 [42 - 102]	246 [48 - 616]
		Number of prescriptions				
		Median (IQR)	4 [1 - 8]	5 [2 - 10]	1 [1 - 2]	3 [1 - 4]
		Initial daily dose, mg				
		Median (IQR)	NA	60 [30 - 100]	20 [9 - 41]	10 [7 - 20]

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IQVIA Germany DA	SIDIAP
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)
		Cumulative daily dose, mg				
		Median (IQR)	NA	2,150 [1,000 - 3,660]	775 [438 - 1,250]	2,250 [430 - 7,100]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)

*Data presented for counts ≥5: prednisone in CDWBordeaux and SIDIAP; prednisolone in CPRD GOLD and IQVIA Germany DA.
IQR: interquartile range, NA: not available

Table 5. Drug utilisation of SLE treatments in adult cohort

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
18+	Azathioprine	**Number of subjects**					
		count (n)	28	134	24	131	224
		Duration, days					
		Median (IQR)	3 [2 - 5]	92 [46 - 360]	30 [8 - 38]	100 [50 - 218]	284 [98 - 1,003]
		Number of prescriptions					
		Median (IQR)	4 [2 - 7]	4 [2 - 11]	2 [1 - 4]	2 [1 - 4]	2 [1 - 4]
		Initial daily dose, mg					
		Median (IQR)	NA	75 [50 - 125]	2 [2 - 50]	100 [75 - 100]	74 [49 - 99]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	<5 (NA%)
		Cumulative daily					

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		dose, mg					
		Median (IQR)	NA	8,400 [4,200 - 30,838]	100 [50 - 250]	10,000 [5,000 - 20,000]	23,387 [7,398 - 85,461]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
18+	Belimumab	**Number of subjects**					
		count (n)	25	0	<5	32	0
		Duration, days					
		Median (IQR)	16 [1 - 30]	NA	NA [NA - NA]	102 [32 - 250]	NA
		Number of prescriptions					
		Median (IQR)	2 [1 - 4]	NA	NA [NA - NA]	2 [1 - 4]	NA
		Initial daily dose, mg					
		Median (IQR)	NA	NA	NA	25 [25 - 29]	NA
		Missing, n (%)	NA	NA	NA	0 (0%)	NA
		Cumulative daily dose, mg					
		Median (IQR)	NA	NA	NA	2,800 [800 - 7,200]	NA
		Missing, n (%)	NA	NA	NA	0 (0%)	NA
18+	Cyclophosphamide	**Number of subjects**					
		count (n)	43	<5	5	0	0
		Duration, days					
		Median (IQR)	72 [30 - 98]	NA [NA - NA]	1 [1 - 18]	NA	NA
		Number of prescriptions					

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Median (IQR)	6 [3 - 6]	NA [NA - NA]	1 [1 - 3]	NA	NA
		Initial daily dose, mg					
		Median (IQR)	NA	NA	NA	NA	NA
		Missing, n (%)	NA	NA	NA	NA	NA
		Cumulative daily dose, mg					
		Median (IQR)	NA	NA	NA	NA	NA
		Missing, n (%)	NA	NA	NA	NA	NA
18+	Cyclosporine	**Number of subjects**					
		count (n)	5	<5	<5	12	23
		Duration, days					
		Median (IQR)	20 [4 - 36]	NA [NA - NA]	NA [NA - NA]	62 [50 - 124]	146 [94 - 490]
		Number of prescriptions					
		Median (IQR)	20 [12 - 36]	NA [NA - NA]	NA [NA - NA]	2 [1 - 4]	2 [2 - 6]
		Initial daily dose, mg					
		Median (IQR)	NA	NA [NA - NA]	NA [NA - NA]	100 [50 - 169]	199 [99 - 275]
		Missing, n (%)	NA	NA (NA%)	NA (NA%)	0 (0%)	0 (0%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	NA [NA - NA]	NA [NA - NA]	5,100 [4,062 - 25,875]	27,250 [21,925 - 96,450]
		Missing, n (%)	NA	NA (NA%)	NA (NA%)	0 (0%)	0 (0%)
18+	Hydroxychloroquine	**Number of subjects**					

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		count (n)	274	639	107	455	1,820
		Duration, days					
		Median (IQR)	4 [3 - 13]	143 [56 - 412]	30 [6 - 60]	59 [50 - 141]	485 [160 - 1,240]
		Number of prescriptions					
		Median (IQR)	6 [3 - 12]	4 [1 - 11]	3 [2 - 7]	1 [1 - 2]	2 [1 - 4]
		Initial daily dose, mg					
		Median (IQR)	NA	400 [200 - 400]	13 [7 - 200]	400 [200 - 400]	199 [197 - 381]
		Missing, n (%)	NA	<5 (NA%)	0 (0%)	0 (0%)	17 (1%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	47,600 [17,300 - 134,400]	600 [400 - 1,400]	20,000 [20,000 - 40,000]	130,051 [36,000 - 333,865]
		Missing, n (%)	NA	<5 (NA%)	0 (0%)	0 (0%)	<5 (NA%)
18+	Methotrexate	**Number of subjects**					
		count (n)	28	145	32	147	372
		Duration, days					
		Median (IQR)	1 [1 - 1]	141 [53 - 338]	76 [30 - 127]	70 [30 - 210]	364 [151 - 839]
		Number of prescriptions					
		Median (IQR)	1 [1 - 2]	6 [2 - 12]	3 [1 - 5]	1 [1 - 2]	3 [1 - 5]
		Initial daily dose, mg					
		Median (IQR)	NA	2 [1 - 2]	0 [0 - 2]	2 [1 - 4]	2 [1 - 4]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)	<5 (NA%)

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Cumulative daily dose, mg					
		Median (IQR)	NA	300 [107 - 744]	32 [2 - 132]	180 [115 - 450]	1,078 [321 - 2,889]
		Missing, n (%)	NA	0 (0%)	0 (0%)	<5 (NA%)	0 (0%)
18+	Mycophenolate mofetil	**Number of subjects**					
		count (n)	64	125	<5	41	139
		Duration, days					
		Median (IQR)	4 [3 - 8]	139 [30 - 477]	NA [NA - NA]	63 [38 - 135]	454 [122 - 1,106]
		Number of prescriptions					
		Median (IQR)	6 [4 - 10]	4 [1 - 16]	NA [NA - NA]	1 [1 - 3]	3 [2 - 5]
		Initial daily dose, mg					
		Median (IQR)	NA	1,000 [625 - 1,500]	NA [NA - NA]	1,000 [1,000 - 1,974]	998 [970 - 1,978]
		Missing, n (%)	NA	0 (0%)	NA (NA%)	0 (0%)	<5 (NA%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	224,000 [42,000 - 837,000]	NA [NA - NA]	75,000 [25,000 - 175,000]	662,500 [159,721 - 1,761,187]
		Missing, n (%)	NA	0 (0%)	NA (NA%)	0 (0%)	<5 (NA%)
18+	Prednisone/ prednisolone*	**Number of subjects**					
		count (n)	243	505	115	556	1,419
		Duration, days					
		Median (IQR)	4 [2 - 13]	7 [5 - 43]	30 [5 - 39]	100 [40 - 139]	111 [31 - 481]

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Number of prescriptions					
		Median (IQR)	4 [2 - 8]	1 [1 - 3]	2 [1 - 5]	1 [1 - 2]	2 [1 - 3]
		Initial daily dose, mg					
		Median (IQR)	NA	40 [28 - 70]	2 [0 - 12]	8 [5 - 20]	9 [5 - 15]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	23 (2%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	400 [200 - 1,000]	20 [5 - 68]	500 [400 - 1,112]	1,038 [300 - 3,951]
		Missing, n (%)	NA	0 (0%)	0 (0%)	0 (0%)	11 (1%)
18+	Rituximab	**Number of subjects**					
		count (n)	49	5	7	5	0
		Duration, days					
		Median (IQR)	15 [9 - 16]	365 [365 - 477]	15 [13 - 25]	30 [30 - 33]	NA
		Number of prescriptions					
		Median (IQR)	4 [2 - 8]	1 [1 - 2]	2 [2 - 3]	1 [1 - 2]	NA
		Initial daily dose, mg					
		Median (IQR)	NA	0 [0 - 0]	1,000 [1,000 - 1,000]	33 [17 - 33]	NA
		Missing, n (%)	NA	0 (0%)	6 (86%)	0 (0%)	NA
		Cumulative daily dose, mg					
		Median (IQR)	NA	100 [100 - 200]	NA [NA - NA]	1,500 [1,000 - 2,000]	NA

Age (years)	Treatment		CDWBordeaux	CPRD GOLD	IMASIS	IQVIA Germany DA	SIDIAP
		Missing, n (%)	NA	0 (0%)	7 (100%)	0 (0%)	NA
18+	Tacrolimus	**Number of subjects**					
		count (n)	18	78	16	13	455
		Duration, days					
		Median (IQR)	8 [4 - 14]	28 [15 - 30]	30 [30 - 53]	30 [30 - 50]	161 [61 - 443]
		Number of prescriptions					
		Median (IQR)	14 [4 - 20]	1 [1 - 1]	2 [1 - 2]	1 [1 - 1]	1 [1 - 3]
		Initial daily dose, mg					
		Median (IQR)	NA	2 [1 - 4]	6 [3 - 9]	2 [1 - 4]	4 [2 - 5]
		Missing, n (%)	NA	66 (85%)	13 (81%)	9 (69%)	368 (81%)
		Cumulative daily dose, mg					
		Median (IQR)	NA	84 [44 - 182]	84 [43 - 161]	337 [237 - 406]	1,327 [278 - 4,711]
		Missing, n (%)	NA	66 (85%)	13 (81%)	9 (69%)	359 (79%)

NA: not available

Discussion

Key results

Our study describes the characteristics and treatment patterns of 11,255 patients with SLE across five electronic health record databases in the UK, France, Spain, and Germany. Among 5,718 new users of SLE treatments, the most frequently prescribed first-line treatments were glucocorticoids and hydroxychloroquine in both the adult and paediatric populations. The most common second-line treatment in children was mycophenolate mofetil and in adults was mycophenolate mofetil and methotrexate. The starting dose of glucocorticoids in children was often higher than in adults. Drug utilisation varied between the databases, particularly with shorter treatment duration and lower doses measured in hospital databases, compared to the primary care databases.

Comparison with existing literature

The predominance of hydroxychloroquine and glucocorticoids as first-line treatments in our study reflects current EULAR treatment guidelines, also seen in drug utilisation studies conducted in other regions, including the USA (9-13), Asia (14-16), Canada (17), and Australia (18).

Previous studies from the UK using CPRD GOLD data showed that half of adult SLE patients started hydroxychloroquine as first-line treatment, and 30% commenced glucocorticoids (19), in line with our study. In Germany, we found lower rates of initiation of hydroxychloroquine (7.5% vs 19.9%) and glucocorticoids (10.8% vs 31%) in adults compared to previous claims-based data (20). A separate study using the German IQVIA DA database estimated between 52-70% of patients were prescribed glucocorticoids in the first 5 years following diagnosis, although estimates from the first year were not available (21). Our estimate of hydroxychloroquine initiation in Spanish patients (both adults and children) with SLE was between 26-41% at 1 year, lower than 81% of Spanish patients attending hospital services enrolled in a prospective multicentre cohort study (22). Drug utilisation data from France is lacking, however one study estimated the prevalence of glucocorticoid use among SLE patients (adults and children) in 2019 at 48% (23).

Few drug utilisation studies in SLE have reported drug dosing, length of treatment, or number of prescriptions, and mostly limited to reporting of glucocorticoids (12, 13, 16, 19, 22-24). An Australian study of adults with SLE, which included similar medications investigated in our study, reported broadly similar initial doses (18).

The percentage of paediatric patients across the databases is lower than 5%, in line with the rarity of the disease, especially under the age of 5 years (25). The median age of the paediatric patients in our study fits within the peak of cSLE onset (12-14 years old) (26). The higher relative proportion of male patients in our paediatric cohort compared to our adult cohort has been observed previously (27). However, most patients were female in both the paediatric and adult cohorts as expected. Sparse data are available on drug utilisation in cSLE patients. In the UK, prospective longitudinal studies of cSLE report 88% of patients received hydroxychloroquine at baseline, and 71% required ongoing systemic glucocorticoids at 1 year post diagnosis, slightly higher than our own estimates for both (62% and 57% respectively) (28, 29). Mycophenolate mofetil was the most common second-line treatment, in line with our data (29).

Strengths and limitations

Our study has a number of strengths. Using five databases allowed us to compare findings between different European countries, with a more representative SLE population. Secondly, our investigation of paediatric cases allowed us to provide evidence of drug utilisation in this population, which is limited in the literature. Our study also provides useful characterisation of SLE in both paediatric and adult patients, providing useful information on disease similarity and its treatment between these populations. A further strength is the use of standardised analytics, allowing the ability to replicate analyses in the future.

Some limitations include: the recording of SLE and co-morbidities varies between databases, often explained by the setting of the database (e.g primary care vs secondary care). For example, we observed higher prevalence of rheumatoid arthritis in IQVIA Germany DA, as most SLE patients in that data source come from rheumatology clinics. While few false positives would be expected, false negatives may occur especially for databases without patient-level linkage from primary to secondary care data. Scarce data are available on the validation of the SLE phenotype in administrative databases in Europe (30, 31). Our study defined SLE using diagnosis codes only and was not based on other clinical data such as symptoms or autoantibody laboratory tests. The recording of treatments may be fragmented and restricted to database care setting. For example, hospital databases may lack outpatient prescriptions and medication history, thus not capture the whole treatment the patient receives, while primary care settings may lack hospital treatments such as monoclonal antibody infusions, both of which we observed in our study. Furthermore, we did not stratify our results by disease severity. For example, severe manifestations such as lupus nephritis, neurologic involvement or pulmonary often required the use of high dose corticosteroids. However, our study did not capture the disease severity of the patients which may influence starting medication and dose.

We used a new user design for drug utilisation to exclude prevalent users, and this excluded patients who started treatment before having a definite diagnosis. This might contribute to the lower percentage of treated patients compared to other studies. The medication dose may be underestimated if the medication code did not contain quantified concepts, such as a ‘box of tablets’ without the actual number of tablets. Also, we could not differentiate whether high doses of steroids were used for acute management of flares or long-term glucocorticoid exposure as it was challenging to distinguish these indications using routinely collected data.

Interpretation

The most frequent first-line treatments in both our study cohorts appeared in line with the European treatment guidelines (4, 5, 7). We observed a small percentage of belimumab and rituximab use in adults in the data sources. Future studies may focus on monoclonal antibodies, especially as new treatments receive market authorisation; and to investigate the availability (marketing and reimbursement) of these treatment options.

In our study, paediatric patients generally received glucocorticoids for longer durations than adult patients, with higher initial dose in some cases. Higher starting doses of oral glucocorticoids in children, compared to adults, have also been reported in other studies (13). Paediatric SLE cohort data from the UK suggest the majority (78%) start oral glucocorticoids at doses of <1mg/kg, however around 30% of the cohort also had intravenous methylprednisolone and therefore may require lower oral starting doses, affecting the mean (29). This steroid burden suggests the need for steroid sparing approaches in cSLE because of the risk of steroid-related adverse effects (32), such as fractures (33). This increased steroid usage may be due to a lack of approved treatments in children.

Conclusions

Our results provide granular detail of the treatment patterns of SLE from primary care and hospital-based databases across four European countries, with findings largely aligning with European SLE treatment guidelines. Our findings provide evidence of some differences in the approach in treating cSLE patients as opposed to adults suggesting a need to further refine treatment guidance in paediatric care.

Contributions

DP-A and EHT led the conceptualisation of the study with contributions from AP and DM. AP-U led the phenotyping of SLE diagnoses. AD and WYM mapped and curated the Clinical Practice Research Datalink (CPRD) GOLD data. GV mapped and curated the Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux) data. MD and MC-S developed the code for statistical analyses with methodological advice from EHT. MD, JTB, NM-B, RG, GV, AL executed study code in the respective databases. DP-A and EHT clinically interpreted the results. FD and EHT wrote the first draft of the manuscript. All authors read, contributed to, and approved the last version of the manuscript. DP-A obtained the funding. MD, MC-S, AD, and WYM had access to and verified the CPRD GOLD data; RG and GV had access to and verified the CDWBordeaux data; JTB had access to and verified the IQVIA data; AL, M-AM, JMR-A had access to and verified the IMASIS data; NM-B and TD-S had access to and verified the SIDIAP data. FD, MD, DP-A, and EHT were responsible for the decision to submit for publication.

The study funder was involved in reviewing the protocol and the objectives, reviewing the results report and contributing to the writing of the manuscript.

Data sharing

Data were obtained from CPRD under the Oxford University CPRD license. Direct data sharing is not allowed. Data access can be obtained from CPRD, conditional on approval through CPRD's Research Data Governance Process.

Ethics approval

For CPRD, the study protocol (23_003161) was approved by the Independent Scientific Advisory Committee for MHRA Database Research (ISAC). The use of IMASIS data was approved by the Hospital del Mar Ethics Committee (protocol 2023/11128). Research Ethics Committee of the University Hospital of Bordeaux approved this study for CDWBordeaux (CER-BDX 2023- 94). For SIDIAP, ethics approval was received by the Clinical Research Ethics Committee of the IDIAPJGol (project code: 23/208-EOm).

Declarations of interest

DPA's department has received grant/s from Amgen, Chiesi-Taylor, Lilly, Janssen, Novartis, and UCB Biopharma. His research group has received consultancy fees from Astra Zeneca and UCB Biopharma. Amgen, Astellas, Janssen, Synapse Management Partners and UCB Biopharma have funded or supported training programmes organised by DPA's department. James Brash and Hanne van Ballegooijen are employees of IQVIA. All other authors have no conflicts of interest to declare.

Acknowledgement

This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by NHS as part of their care and support programme. The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being

made on behalf of or reflecting the position of the regulatory agency/agencies or organisations with which the author(s) is/are employed/affiliated.

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