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ORIGINAL RESEARCH

The Impact of Systemic Lupus Erythematosus Flares on Clinical and Economic Outcomes: The CHAMOMILE Claims Database Study in Germany

Bo Ding · Marc Pignot · Elena Garal-Pantaler · Beate Villinger · Sebastian Schefzyk · Barnabas Desta · Heide A. Stirnadel-Farrant · Andreas Schwarting

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ABSTRACT

Introduction: CHAMOMILE (CHaracteristics and impact of flares on clinicAl and econoMic OutcoMes In patients with systemic Lupus Erythematosus [SLE]) examined how flares in the year of SLE diagnosis impact future disease activity and damage, productivity, healthcare resource utilization (HCRU), and costs in patients with SLE in Germany.

Methods: CHAMOMILE was a retrospective cohort study of adults with an SLE diagnosis in the German Sickness Fund Database from 1 July 2010 to 31 December 2013. Patients were classified according to their greatest flare severity during the baseline year (none, mild, or moderate/severe). The number and severity of flares were assessed annually over 5–8.5 follow-up years, along with SLE organ/system damage, treatments, work disability, and HCRU metrics.

Results: Of 2088 patients (84.6% female; mean age [standard deviation] 51.4 [16.1] years; mean follow-up 6.8 [2.1] years), 34.3% (n = 716) were flare-free, 29.8% (n = 622) had mild flares, and 35.9% (n = 750) had moderate/severe flares at baseline. Baseline flare severity was related to

Prior Presentation: Partial data from this study has been presented at Deutscher Rheumatologiekongress (DGRh DocEV.27; 31 August–3 September 2022; Berlin, Germany) and the Annual European Congress of Rheumatology (EULAR POS1403; 1–4 June 2022; Copenhagen, Denmark).

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B. Ding (✉)
BioPharmaceuticals Medical, AstraZeneca, Pepparedsleden 1, 431 83 Mölndal, Sweden
e-mail: Bo.Ding@astrazeneca.com

M. Pignot
Center of Epidemiology and Health Research Berlin, ZEG Berlin GmbH, Berlin, Germany

E. Garal-Pantaler
Health Economics Department, Team Gesundheit GmbH, Essen, Germany

B. Villinger · S. Schefzyk
BioPharmaceuticals Medical, AstraZeneca, Hamburg, Germany

B. Desta
BioPharmaceuticals Business Unit, AstraZeneca, Gaithersburg, MD, USA

H. A. Stirnadel-Farrant
Oncology Business Unit Medical, AstraZeneca, Cambridge, UK

A. Schwarting
Center for Rheumatic Disease Rhineland-Palatinate, Bad Kreuznach, Germany

A. Schwarting
Rheumatology and Clinical Immunology, University Medicine of Johannes Gutenberg University Mainz, Mainz, Germany

future flares: rates during follow-up were higher in patients with moderate/severe baseline flares compared with those with mild or no baseline flares (89.6 vs 78.5 and 44.2 flares/100 patient years, respectively). Overall, 80.2% (n = 1675) of patients received glucocorticoids at least once during baseline and follow-up. Patients' HCRU was generally greatest in their baseline year. Costs were highest in patients with moderate/severe baseline flares.

Conclusion: Baseline flare severity provided insight into a patient's disease course and the clinical and economic burden of SLE over time, highlighting the ramifications of uncontrolled disease for patients with SLE.

Keywords: Flare; Glucocorticoids; Healthcare resource utilization; Systemic lupus erythematosus

Key Summary Points

Why carry out this study?

Patients with systemic lupus erythematosus (SLE) can experience substantial adverse clinical, economic, and social outcomes at the time of diagnosis and over the course of disease.

CHAMOMILE (CHaracteristics and impact of flares on clinicAl and econoMic OutcoMes In patients with systemic Lupus Erythematosus) examined how flares in the year after diagnosis relate to the frequency and severity of flares over time in patients with SLE in Germany.

What was learned from the study?

By utilizing a large patient database to follow patients for up to 8.5 years, the CHAMOMILE study was able to present a detailed description of the clinical course of SLE for patients receiving standard therapy in Germany.

Patients with more severe flares in their first year after SLE diagnosis experienced more subsequent flares and more flares of higher severity, averaged greater daily oral glucocorticoid use, and accumulated more damage annually than patients with no or mild baseline flares over multiple follow-up years.

SLE flares in the first year after diagnosis can provide insight into subsequent disease activity, glucocorticoid use, cumulative organ damage, and healthcare resource utilization and costs.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a variable disease course, with periods of increased disease activity (flares) followed by periods of disease remission [1]. Patients with SLE can experience substantial adverse clinical, economic, and social outcomes [2–4]; greater disease severity has been associated with the occurrence of flares as well as increased healthcare utilization and costs [2, 5].

Glucocorticoids are effective for short-term symptom relief in patients with SLE owing to their ability to reduce inflammatory disease activity [6]. However, long-term glucocorticoid exposure contributes to adverse events and organ damage (e.g., cutaneous, musculoskeletal, renal, ocular, and/or gastrointestinal system damage), with these effects related to patients' cumulative glucocorticoid dose [7–9]. Limiting glucocorticoid dosage, especially to less than 5 mg/day, can reduce future organ damage, as proposed in the European Alliance of Associations for Rheumatology (EULAR) recommendations for SLE treatment [10–12].

There are limited data regarding longitudinal outcomes and healthcare utilization/costs associated with SLE flares in Germany. Here, we aim to characterize the frequency, severity, and organ system involvement of flares in patients

with SLE in Germany and to examine how flares in the baseline year can impact future disease activity, productivity, health care resource utilization (HCRU), and costs in patients with SLE.

METHODS

Study Design and Patients

CHAMOMILE (CHaracteristics and impact of flares on clinicAl and econoMic OutcoMes In patients with systemic Lupus Erythematosus) was a retrospective cohort study of adults with SLE in the Betriebskrankenkassen (BKK) German Sickness Fund Database [13]. Patients were included in the study if they had SLE (International Classification of Diseases code ICD-10-German Modification) and were at least 18 years of age during their index year (Fig. 1a). Patients with diagnoses of drug-induced SLE in the identification period were excluded.

The patient identification period was 1 July 2010–31 December 2013. A patient's baseline period started at the beginning of the quarter of their earliest SLE diagnosis during the identification period and included 1 year. To exclude patients misclassified with SLE, the internal diagnosis validation algorithm elaborated in Schwarting et al. [13] was used; therefore, patients must have had records in the BKK for six quarters prior to index (i.e., for 6 months preceding their baseline year). Patients were followed from their index date until death, migration outside of the database, or end of study (31 December 2019), whichever was first.

Ethical Approval

All patients who met inclusion criteria were included in the study. Use of the BKK database for health services research is fully compliant with German federal law; health insurance companies were informed of the project, and required approvals were received from BKK. The study conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. Informed consent by patients was not necessary and institutional review board/ethical approval was not required, as these claims data are de-identified.

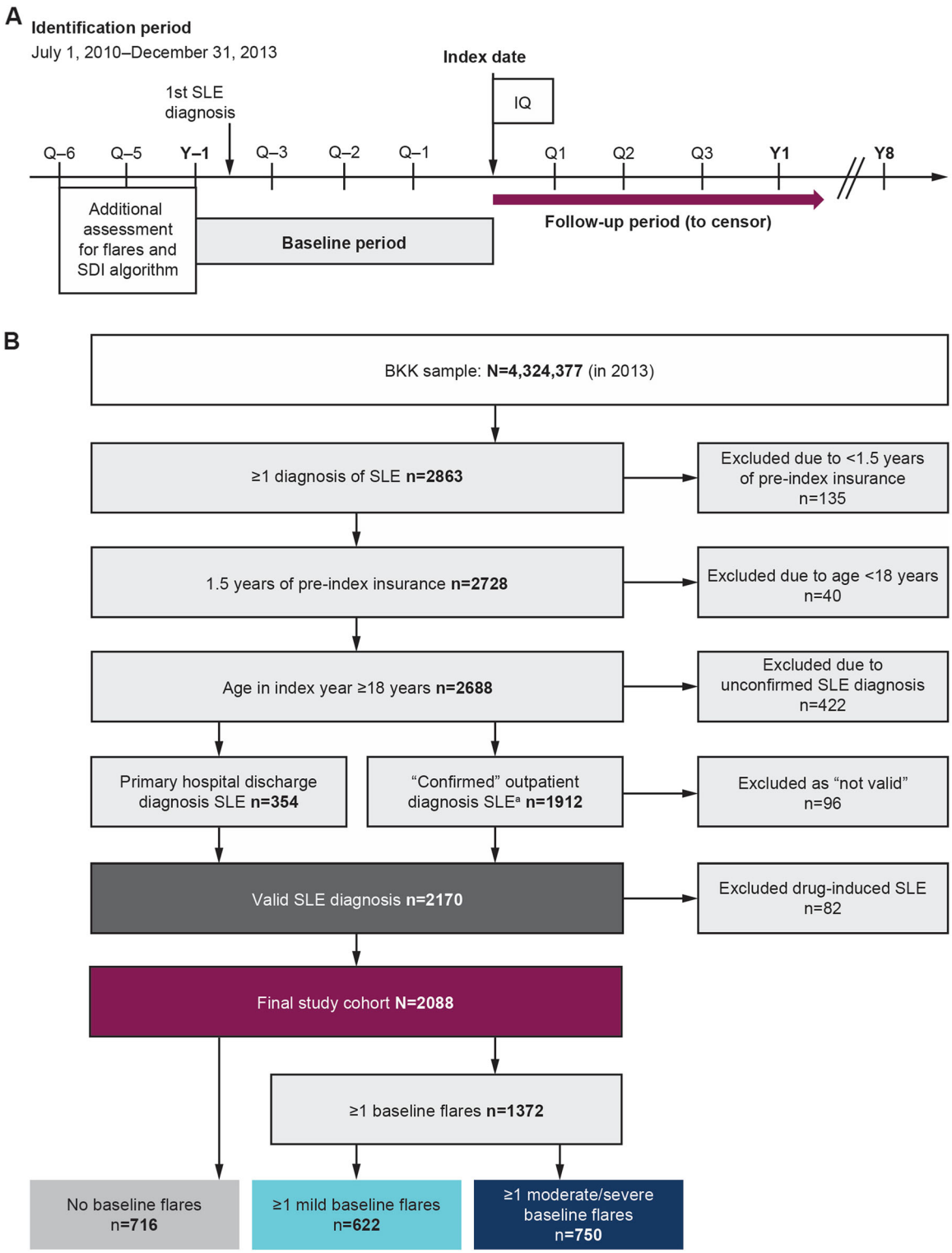
Classification of SLE Flares and Flare Severity

SLE flares were defined using a claims-based algorithm adapted from Garris et al. [2] and further refined in collaboration with medical experts. Newly prescribed SLE-relevant medication or change of therapy in the direction of stronger agents or higher dosages was assumed to be a response to disease exacerbation and was therefore considered a flare. Indicators of flare included oral glucocorticoid dose increases of at least a factor of 2; injectable glucocorticoid prescriptions with dosage of at least 100 mg prednisone equivalents; a new prescription of a non-steroidal anti-inflammatory drug (NSAID), antimalarial, immunosuppressant (cyclophosphamide, mycophenolate mofetil, methotrexate, ciclosporin A, tacrolimus, or leflunomide), or other injectable steroid; hospitalization with SLE as a primary diagnosis for at least 7 days; and/or hospitalization with SLE flare-related conditions as primary diagnoses for 7 days or more.

Patients were classified into three groups according to the greatest severity of flare experienced during the baseline period: no flares, mild (i.e., only mild flare[s] during baseline), or moderate/severe (i.e., at least one moderate and/or severe flare during baseline). (See Table S1 in the electronic supplementary material for a full description of the differences between baseline flare categories.)

Baseline Variables and Study Outcomes

Baseline demographics, SLE-related clinical manifestations, comorbidities, disease severity, and medication use were summarized. SLE disease severity (mild, moderate, or severe) was assigned according to the algorithm elaborated in Schwarting et al. [13] that considers SLE manifestation severity and therapy.


A
Identification period
July 1, 2010–December 31, 2013
Index date
1st SLE diagnosis
IQ
Q–6
Q–5
Y–1
Q–3
Q–2
Q–1
Q1
Q2
Q3
Y1
Y8
Additional assessment for flares and SDI algorithm
Baseline period
Follow-up period (to censor)
B
BKK sample: N=4,324,377 (in 2013)
≥1 diagnosis of SLE n=2863
Excluded due to <1.5 years of pre-index insurance n=135
1.5 years of pre-index insurance n=2728
Excluded due to age <18 years n=40
Age in index year ≥18 years n=2688
Excluded due to unconfirmed SLE diagnosis n=422
Primary hospital discharge diagnosis SLE n=354
"Confirmed" outpatient diagnosis SLE[a] n=1912
Excluded as "not valid" n=96
Valid SLE diagnosis n=2170
Excluded drug-induced SLE n=82
Final study cohort N=2088
≥1 baseline flares n=1372
No baseline flares n=716
≥1 mild baseline flares n=622
≥1 moderate/severe baseline flares n=750

◀**Fig. 1** CHAMOMILE study design. **a** Representation of CHAMOMILE patients' index date, baseline period, and follow-up periods; **b** flowchart of patients from BKK database through final study cohort and baseline flare subgroups. [a]Of patients with confirmed outpatient SLE diagnosis, 1334 were diagnosed by a specialty physician, 1152 had laboratory tests for SLE diagnosing and control, 1597 received SLE-relevant medication (antimalarials, corticosteroids, or immunosuppressants), and 377 had SLE-relevant organ system involvement. *BKK* Betriebskrankenkassen German Sickness Fund Database, *IQ* index quarter, *Q* quarter, *SDI* Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, *SLE* systemic lupus erythematosus

Outcomes were assessed each year over at least 5, and up to 8.5, follow-up years and compared with patients' baseline year. These outcomes included SLE manifestation-related comorbidities; cumulative damage index (proxy SDI, developed in Schultze et al. [14] and further adapted here) as a proxy for the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; organ damage assessed by SLICC/ACR Damage Index domain [15]; cumulative dose of systemic glucocorticoids; work disability [days of sick leave]; HCRU variables [hospital admissions, ambulant treatments, outpatient visits/prescriptions, other benefits {includes additional services paid by insurance funds such as transportation and administrative costs; preventive care, cure, and courses; and psychotherapy, etc.}]; and costs per person-year (PPY).

Statistical Analysis

Descriptive statistics were used. For continuous variables, results are presented in terms of mean, standard deviation (SD), standard error (SE), median, range and/or percentile of values.

RESULTS

Patients

After inclusion/exclusion criteria were applied to the 2863 patients identified with at least one SLE diagnosis between 1 July 2010 and 31 December 2013, 2088 patients were included (Fig. 1b). Most patients were female (n = 1767, 84.6%) with a mean (SD) age at index of 51.4 (16.1) years and duration of patient follow-up of 6.8 (2.1) years. At baseline, more patients had baseline SLE disease severity categorized as moderate (n = 849, 40.7%) or severe (n = 739, 35.4%) than mild (n = 500, 24.0%), and more than half of patients (n = 1144, 54.8%) were receiving glucocorticoid treatment (Table 1). At baseline, 34.3% (n = 716) of patients were considered flare-free, 29.8% (n = 622) had mild flares, and 35.9% (n = 750) had moderate/severe flares. The mean (SD) age at baseline was 50.9 (15.7), 50.5 (16.0), and 52.7 (16.6) years for patients with mild, moderate/severe, or no baseline flares, respectively. A total of 210 patients (10.1%) died during the study, and 263 (12.6%) were lost to follow-up.

Flares

Overall, including at baseline year and during 8 years or more of follow-up, 11,175 flares were identified, with 95.7% (n = 1998) of patients experiencing at least one flare (Table 2). The rates of mild, moderate, and severe flares were 40.6, 20.7, and 9.1 flares per 100 patient years (PY), respectively. Patients with moderate/severe or mild flares at baseline had more subsequent flares than patients with no baseline flares (moderate/severe, 44.6% [n = 4984]; mild, 33.5% [n = 3749]; no flares, 21.9% [n = 2442]). Flare rates were higher in patients with moderate/severe flares at baseline compared with those who had mild or no flares (89.6 vs 78.5 and 44.2 flares/100 PY, respectively). Similarly, severe flare rates were higher in patients with moderate/severe versus mild/no flares at baseline (severe flare rate per 100 PY = 16.8 vs 5.2 and 4.7 in the mild and no baseline flare groups, respectively) (Table 2). The median (range) interval between flares in an individual patient was 309 (46–3460) days (see Table S2 in the electronic supplementary material for details).

Glucocorticoid Use

Overall, 80.2% (n = 1675) of patients received systemic glucocorticoids at least once during

Table 1 Patient characteristics by flares at baseline

	Total	Flare group at baseline		
		No flares	Mild	Moderate/severe
Group size, *n* (%)	2088	716 (34.3)	622 (29.8)	750 (35.9)
Female, *n* (%)	1767 (84.6)	594 (83.0)	547 (87.9)	626 (83.5)
Age, mean (SD), years	51.4 (16.1)	52.7 (16.6)	50.9 (15.7)	50.5 (16.0)
Manifestations, *n* (%)				
Any	1922 (92.1)	643 (89.8)	570 (91.6)	709 (94.5)
Cutaneous	1394 (66.8)	444 (62.0)	419 (67.4)	531 (70.8)
Osteoarticular	600 (28.7)	153 (21.4)	172 (27.7)	275 (36.7)
Vascular	480 (23.0)	146 (20.4)	124 (19.9)	210 (28.0)
Ophthalmological	432 (20.7)	139 (19.4)	140 (22.5)	153 (20.4)
Renal	415 (19.9)	129 (18.0)	81 (13.0)	205 (27.3)
Neuropsychiatric/neurological	323 (15.5)	91 (12.7)	94 (15.1)	138 (18.4)
Respiratory	263 (12.6)	73 (10.2)	59 (9.5)	131 (17.5)
SLE treatment, *n* (%)				
Glucocorticoids	1144 (54.8)	173 (24.2%)	313 (50.3%)	658 (87.7%)
Antimalarials	840 (40.2)	173 (24.2%)	322 (51.8%)	345 (46.0%)
NSAIDs	816 (39.1)	113 (15.8%)	386 (62.1%)	317 (42.3%)
Immunosuppressants	714 (34.2)	158 (22.1%)	119 (19.1%)	437 (58.3%)
Biologics	30 (1.4)	0	1 (0.16%)	29 (3.9%)
Disease severity, *n* (%)				
Mild	500 (24.0)	261 (36.5)	212 (34.1)	27 (3.6)
Moderate	840 (40.2)	247 (34.5)	239 (38.4)	354 (47.2)
Severe	748 (35.8)	208 (29.1)	171 (27.5)	369 (49.2)
Proxy SDI, mean (SD)	2.5 (2.3)	2.4 (2.2)	2.2 (2.2)	2.8 (2.4)

NSAIDs non-steroidal anti-inflammatory drugs, *SD* standard deviation, *proxy SDI* Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, *SLE* systemic lupus erythematosus

baseline and follow-up; of these patients, 96.8% ($n = 1622$) received oral glucocorticoids. Systemic glucocorticoid use was seen in a higher proportion of patients with moderate/severe baseline flares vs those with mild or no flares (96.0% vs 77.8% and 65.8%, respectively; see Table S3 in the electronic supplementary material for details). The mean cumulative daily oral glucocorticoid dose exceeded 5 mg prednisone or equivalent in the moderate/severe baseline flare group in every follow-up year except year 4 (range 4.9–7.7 mg) (Fig. 2a), while patients in the mild baseline flare group had the lowest mean cumulative daily oral glucocorticoid doses in every follow-up year (range 3.6–4.4 mg). Mean cumulative daily oral

Table 2 Flare occurrence over the entire study period by baseline flare severity

	n	Patients with ≥ 1 flare, *n* (%)	Total number of flares	Number of flares per 100 PY	Number of flares per 100 PY by flare severity		
				Overall	Mild	Moderate	Severe
All patients	2088	1998 (95.7)	11,175	70.5	40.6	20.7	9.1
Baseline flare exposure[a,b]							
No flares	716	631 (88.1)	2442	44.2	28.5	11.0	4.7
Mild flares	622	621 (99.8)	3749	78.5	60.8	12.6	5.2
Moderate/severe flares	750	746 (99.5)	4984	89.6	35.4	37.4	16.8

PY patient-years, *SLE* systemic lupus erythematosus

Study period includes baseline year and up to 8 years of follow-up

[a]The baseline period started at the beginning of the first quarter with a diagnosis of SLE during the identification period and spanned 1 year

[b]A flare was defined as every newly prescribed SLE-relevant medication (e.g., non-steroidal anti-inflammatory drugs, antimalarials, immunosuppressants, other injectable steroid application) or every change of therapy in the direction of stronger agents/higher dosages

glucocorticoid doses exceeded 5 mg at baseline and follow-up years 2 and 6 (range 4.2–5.8 mg) in patients with no baseline flares; during these years, mean cumulative daily doses were higher in the no baseline flare group than in the mild flare group (Fig. 2a).

Cumulative Damage Index (Proxy SDI) and Organ System Damage

Organ damage in the overall cohort, assessed using mean (SD) proxy SDI, increased from 2.5 (2.3) at baseline to 4.1 (3.2) in the fifth follow-up year. Mean proxy SDI was higher in patients with moderate/severe baseline flares than in other flare categories across all study years (Fig. 2b). The rate of proxy SDI increase was similar regardless of baseline flare severity. Mean annual proxy SDI increased with both the cumulative number (across baseline and follow up) and severity of flares (see Fig. S1 in the electronic supplementary material for details).

In the two quarters preceding baseline, 13.0% (n = 272) of patients had a history of damage in at least one SLICC/ACR damage index domain [15]. Overall, 72.0% (n = 1503) of patients experienced organ damage during their baseline period. By the end of follow-up year 5, organ damage was recorded in 93.7%, 94.1%, and 96.9% of patients with no, mild, or moderate/severe baseline flare exposure (n = 671, n = 585, and n = 727 of 1983), respectively. The proportions of patients with damage increased from baseline to year 5 across all domains, regardless of baseline flare exposure (see Fig. S2 in the electronic supplementary material for details); in follow-up year 5, damage was most common in the cutaneous (71.3%, n = 1488), musculoskeletal (43.5%, n = 908), and ocular (40.3%, n = 841) domains. The greatest relative changes in proportion of patients with damage from baseline to year 5 were in the gastrointestinal, gonadal, ocular, neuropsychiatric, and cardiovascular domains, in which the proportion of patients with involvement all at least doubled; the smallest relative change was in the proportion of patients with cutaneous domain involvement, which increased 0.25-fold.

Work Disability

At baseline, mean (SD) total days of employment missed because of disability was 27.3 (80.6) days in the moderate/severe baseline flare group,

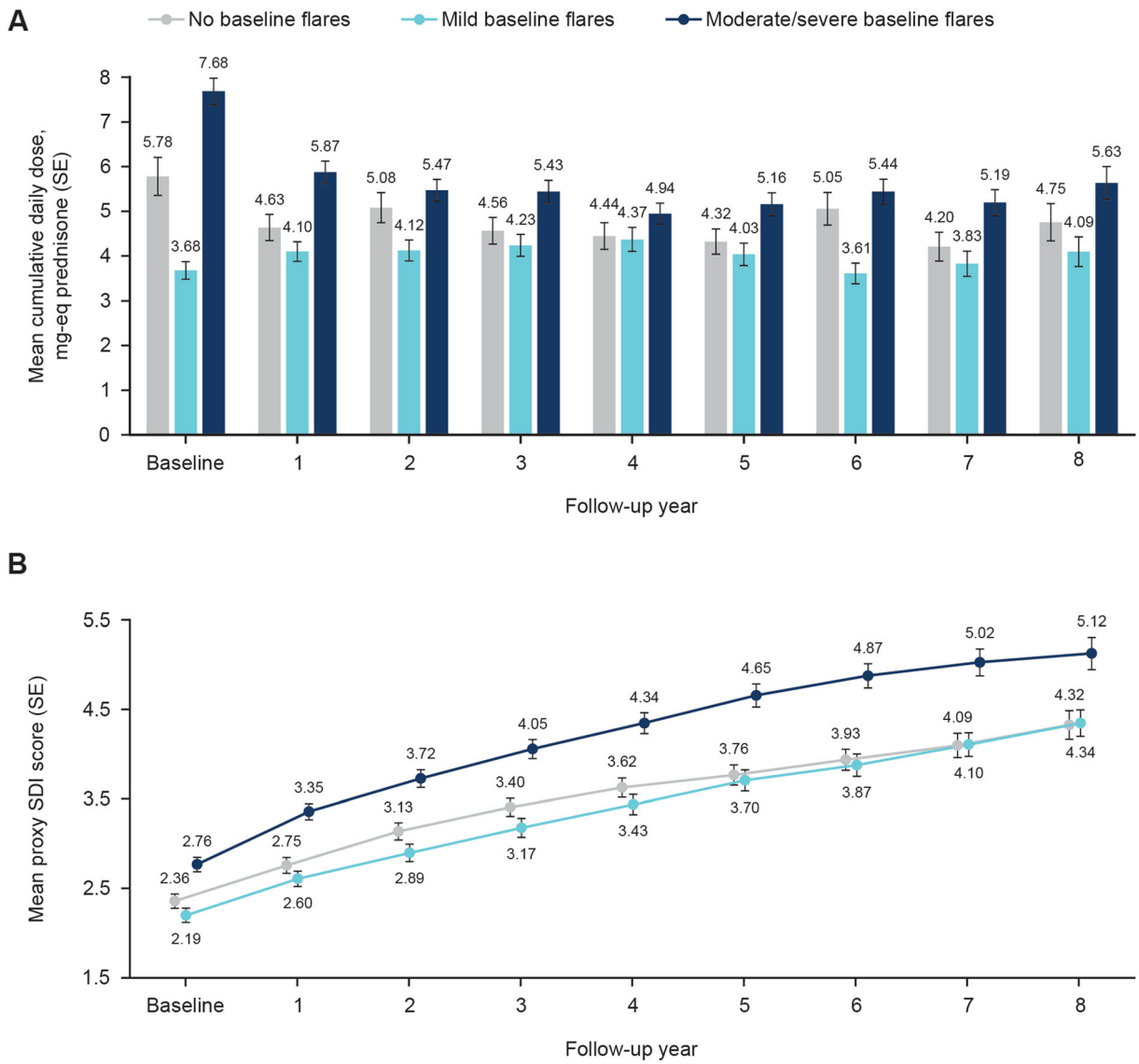


Fig. 2 Annual cumulative organ damage and daily glucocorticoid doses over time by baseline flares. **a** Bar graph showing annual cumulative daily dose of oral glucocorticoid (mg-equivalent of prednisone); **b** line graph showing annual cumulative damage index scores (proxy SDI). Data are presented as mean ± standard error. *eq* equivalent, *SDI* Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, *SE* standard error

while the no and mild baseline flare groups averaged 11.3 (44.8) and 13.8 (49.4) days, respectively (Table 3). Similarly, patients with moderate/severe baseline flares averaged more total days of long-term disability than the other flare groups (moderate/severe 9.8 [54.4] days vs no flares 3.9 [31.8] days and mild 4.5 [35.9] days). After 8 years of follow-up, the mean total days of work disability were similar to baseline in the mild and moderate/severe baseline flare groups, and patients in the no baseline flare group had, on average, fewer total days of work disability, compared with baseline (Table 3).

Table 3 Work disability and healthcare resource use at baseline and follow-up year 8 by baseline flares

Mean (standard deviation)	Baseline				Follow-up year 8			
	Total	No flare	Mild flare	Moderate/severe flare	Total	No flare	Mild flare	Moderate/severe flare
	N = 2088	*n* = 716	*n* = 622	*n* = 750	*n* = 1183	*n* = 444	*n* = 348	*n* = 391
Disability								
Total days of work disability	17.8 (61.6)	11.3 (44.8)	13.8 (49.4)	27.3 (80.6)	10.5 (48.0)	7.1 (24.8)	12.5 (55.7)	12.7 (59.3)
Total days of long-term disability	6.2 (42.4)	3.9 (31.8)	4.5 (35.9)	9.8 (54.4)	4.1 (36.0)	2.1 (15.9)	5.8 (47.1)	4.9 (40.8)
Hospital admission								
Number of hospital stays	0.8 (2.1)	0.5 (2.7)	0.5 (0.9)	1.4 (2.0)	0.5 (1.1)	0.4 (0.9)	0.5 (0.9)	0.5 (1.3)
Length of hospital stays, days	7.6 (20.3)	3.5 (13.0)	4.6 (15.8)	13.9 (26.7)	4.7 (17.7)	4.1 (13.5)	4.2 (13.6)	5.9 (23.9)
Ambulant treatments in hospital								
Number of ambulant hospital visits	0.5 (1.1)	0.3 (0.8)	0.5 (1.0)	0.7 (1.3)	0.6 (1.3)	0.5 (1.1)	0.5 (1.2)	0.8 (1.5)
Outpatient visits								
Number of outpatient visits	39.2 (29.5)	33.3 (30.5)	36.8 (23.5)	46.7 (31.4)	31.5 (33.2)	33.4 (43.7)	29.3 (22.0)	31.3 (27.0)
Outpatient prescriptions								
Number of outpatient prescriptions	24.2 (21.5)	19.6 (19.2)	21.1 (20.4)	31.0 (22.8)	21.7 (21.2)	20.6 (22.6)	20.4 (19.6)	24.0 (20.8)
Other benefits								
Number of other benefits utilization	3.2 (6.7)	2.5 (5.3)	2.7 (5.4)	4.2 (8.6)	12.4 (35.1)	12.3 (32.1)	11.1 (29.0)	13.8 (42.7)
Cost of other benefits, €[a]	675.87 (2089.23)	555.79 (1778.11)	558.08 (1691.49)	888.18 (2588.73)	1055.65 (2934.28)	1050.89 (2632.10)	1086.66 (3487.30)	1033.47 (2720.97)

Means and standard deviations are calculated per capita in the entire subgroup of patients that have at least one day of insurance in the follow-up year

[a]Deflated to the last study year, 2019

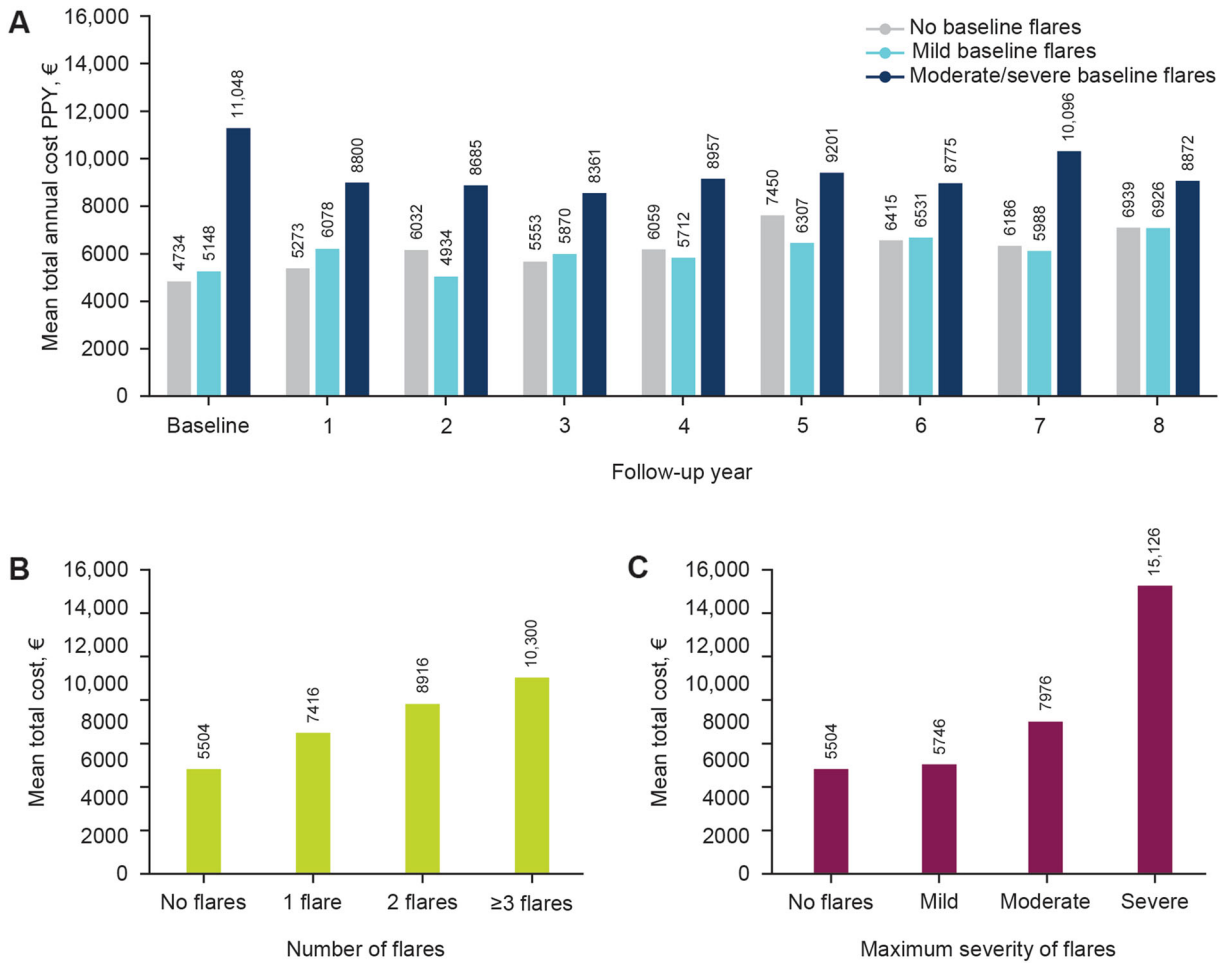


Fig. 3 Mean total annual healthcare costs, in euros, per patient year annually by baseline flares and by greatest number and severity of flares in that year. Bar graphs show **a** total annual healthcare costs annually per patient year by baseline flares; **b** total annual healthcare cost by number of flares in that year, regardless of severity; **c** total annual healthcare cost by greatest flare severity experienced by a patient in that year. All available follow-up years were stratified by the number of flares or maximal flare severity in the corresponding year. Note that flare could be attributed to corresponding year by onset date and it was not possible to define the end of flare by means of claims data. Means are presented. *PPY* per patient year, *SLE* systemic lupus erythematosus

Healthcare Resource Utilization

For all measures of baseline HCRU, mean (SD) values were lowest for the no baseline flares group and highest for the moderate/severe baseline flare group (Table 3). Hospital stays averaged 13.9 (26.7) days for patients with moderate/severe baseline flares, while stays for patients with no or mild baseline flares averaged less than a week (3.5 [13.0] and 4.6 [15.8] days, respectively) (Table 3). For most HCRU measures, mean values were lower after 8 years of follow-up than at baseline, regardless of baseline flare exposure (Table 3).

However, the number and costs of other benefits utilizations were higher at year 8 than at baseline for all baseline flare groups. Baseline mean (SD) cost of other benefits was €555.8 (1778.1), €558.1 (1691.5), and €888.2 (2588.7) for the no flares, mild flare, and moderate/severe baseline flare groups, respectively, and year 8 mean (SD) costs were €1050.9 (2632.1),

€1086.7 (3487.3), and €1033.5 (2721.0) (Table 3).

Patient Costs

Overall, total annual costs accrued by patients with SLE decreased slightly from €7125 per PY in the baseline period over the next 3–4 years (€6775 to €6974), then gradually increased to €7568 in follow-up year 8. Annual costs per PY by baseline flare exposure are shown in Fig. 3a. At baseline, patients with moderate/severe baseline flares had at least twofold higher annual cost vs those with no or mild flares. Costs were similar in patients with no or mild flares, with costs increasing gradually over time. Costs in patients with moderate/severe flares decreased from €11,048 to €8800 in follow-up year 1 and then remained relatively constant through follow-up year 8. Mean total annual healthcare costs increased by number of baseline flares in that year, regardless of flare severity (Fig. 3b), but annual costs were greater for patients who experienced severe flare in that year (€15,126; Fig. 3c), compared to those who experienced no flares (€5504), or a highest flare severity of mild or moderate (€5746 or €7976).

DISCUSSION

Patients with SLE are faced with long-term clinical and economic burdens that substantially impact their quality of life and can also indirectly impact society [16, 17]. To fully understand the extent of the global burden of SLE, information must be evaluated across a range of patient populations and healthcare systems. As SLE is a chronic, progressive disease that can lead to irreversible organ damage [18] and increased long-term mortality risk [19], evaluations of disease burden should follow patients over many years to assess how disease progression affects resource utilization over time. The German BKK health insurance fund database [13], one of the country's largest sickness funds with long-term records, allowed for such an evaluation; here, the CHAMOMILE study utilized the database to identify a large cohort of patients with up to 8 years of follow-up to characterize the longitudinal clinical and economic impacts of SLE flares in Germany. Flares during a patient's first year of SLE diagnosis were associated with incidence and severity of future flares, glucocorticoid use, work-related productivity, HCRU, and costs, highlighting the importance of controlling flares and minimizing long-term glucocorticoid use in patients with SLE.

Greater baseline disease severity has been associated with increased likelihood and severity of SLE flares over the short term [2]. In the CHAMOMILE cohort, degree of baseline flare severity was related to patients' future experiences with flares over the 8 years or less of follow-up. On average, patients who experienced moderate/severe baseline flares experienced a greater number of and more severe flares over the study than patients with no or mild baseline flares.

Possibly as a result of their baseline flare status, patients with moderate/severe baseline flares experienced greater glucocorticoid exposure. Guidelines for maintenance treatment recommend that patients taper daily glucocorticoid use to 5.0 mg or less if full withdrawal is not possible [11, 12], and 5.0 mg/day or less is considered a goal for clinical remission on treatment [20]. However, in CHAMOMILE patients with moderate/severe baseline flares, annual mean cumulative daily oral glucocorticoid dose exceeded 5.0 mg in every year of the study except year 4, suggesting that they were not able to taper glucocorticoids completely.

Of note, cumulative glucocorticoid dosages were higher in patients with no vs mild baseline flares in every study year. It is important to point out that "no flare at baseline" is not equivalent to "no disease activity". Compared with the mild flare group, the no baseline flare group included more patients with renal manifestations, more using immunosuppressants, and more with severe SLE; mean SDI was higher in the no baseline flare group, as were the proportions of patients with renal, cardiovascular, and peripheral vascular damage. While the retrospective nature of our analysis limits our conclusions, some patients in the no flare group may have had severe (e.g., renal) manifestations in the past requiring high-dose glucocorticoid

or immunosuppressant therapy. Our findings highlight the challenges of balancing the treatment goals of minimizing disease activity and preventing flares while maintaining the lowest possible glucocorticoid dose when increasing glucocorticoid dose remains an important tool for treating flares [11].

Flares, high disease activity, and increased glucocorticoid use contribute to organ damage in patients with SLE [8, 21, 22]. As expected because of the irreversible nature of organ damage [8], mean damage scores increased from baseline over time in all baseline flare subgroups. At baseline and for each of the 8 follow-up years, annual damage scores were highest in patients who experienced moderate/severe baseline flares, compared with patients with no or mild flares. After 5 years of follow-up and standard SLE treatment, the proportions of patients with organ/system involvement increased from baseline in every domain, doubling in gastrointestinal, gonadal, ocular, neuropsychiatric, and cardiovascular domains, suggesting a continued unmet need for adequate treatments that do not contribute to organ damage.

More severe SLE has been associated with higher HCRU and costs in numerous patient populations [23, 24]. In addition to costs associated with treating SLE, employment rates among patients with SLE tend to be lower than in the general population, and work disability is common [3, 16], providing additional economic burden. Consistent with these trends, in this cohort, patients with moderate/severe baseline flares experienced more days of work disability and more and longer hospital stays during the baseline year and in the eighth year of follow-up than patients with mild or no baseline flares. A previous German claims study using the BKK database found that moderate and severe SLE was associated with significantly higher HCRU and costs vs matched controls [13]. Although that study compared costs across 5 years by disease severity and the current study compared costs across 8 years by baseline flare severity, mean annual all-cause costs per capita were similar for patients with severe disease and those with moderate/severe baseline flares (approx. €8–11,000), supporting an association between disease activity and healthcare costs in this database.

As a result of their intermittent nature and the level of clinical detail required to measure flares, there are limited long-term assessments of the impact of SLE flares on HCRU outcomes and cost. Two studies of claims databases from the USA demonstrated that increased disease severity was associated with increased flare rates, greater HCRU, and higher costs [2, 5]. A retrospective observational study of patient medical records in Europe identified the annual number of severe SLE flares as the strongest predictor of medical costs, with annual costs almost doubling with each severe flare [24]. Here, severe flares were defined in part by hospital admission and, in the USA, inpatient costs were found to be the main all-cause cost driver within 90 days of a severe flare [5]. In our study, the mean total annual cost for patients with moderate/severe flares at baseline was more than twice that of patients with no flares. That patients with moderate/severe flares in their first year of SLE diagnosis continued to have higher average annual costs than patients with no or mild baseline flares across 8 years of follow-up reinforces the unmet need for effective treatments for SLE. Of note, annual costs also increased with the number of annual flares that year, highlighting the potential burden of any flare for a patient, irrespective of flare severity.

A strength of the current study is that it refines the algorithms used in the previous BKK study [13], expanding patient selection to include more patients and a longer follow-up period. Utilizing this very large patient database in this way allows for a more accurate description of the clinical course of SLE, a disease with highly variable presentation [3], and improves our ability to assess cumulative organ damage due to disease activity and glucocorticoid use.

This study has a few limitations. The cohort included 2088 patients with SLE, but these patients were all receiving treatment in Germany, and so the results may not be generalizable to other countries, especially those outside of the European Union. Additionally, outcomes were based on insurance reimbursement data, which are likely to be less complete than medical records/patient charts. Treatments included

in the study were restricted to those prescribed for outpatient use and cumulative and daily glucocorticoid dosages were estimated on the basis of prescription claims, which cannot account for patient adherence. Examining the relationship between flare severity and economic burden is complicated by the inclusion of medication use and hospitalization in the definitions of the flare categories, which are inherently costly. However, the greater burden of more severe flares for patients with SLE extended beyond medication use and hospitalization to other HCRU measures and work disability, and continued for up to 8 years, highlighting the burden of moderate and severe flares for patients with SLE.

CONCLUSION

In this long-term cohort study, baseline flare severity provided insight into a patient's disease course and the clinical and economic burden of SLE over time. Patients with more severe flares in their first year of SLE experienced more subsequent flares and more flares of higher severity, averaged greater daily oral glucocorticoid use, and accumulated more damage annually than patients with no or mild baseline flares over multiple follow-up years. These results highlight the ramifications of uncontrolled disease and glucocorticoid use for patients with SLE and the health systems on which they depend.

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Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request. The data may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Declarations

Conflict of Interest. Andreas Schwarting has received research grants from Novartis, GSK, and Roche; consulting fees from Kantar Health, and honoraria for presentations from GSK, Novartis, and AstraZeneca. Heide A. Stirnadel-Farrant has stock or stock options in GSK. Barnabas Desta, Bo Ding, and Heide A. Stirnadel-Farrant are employees of AstraZeneca and have AstraZeneca stock or stock options. Sebastian Schefzyk is an employee of AstraZeneca. Marc Pignot is an employee of ZEG-Berlin, which was funded by AstraZeneca to conduct the study. Elena Garal-Pantaler is an employee of Team Gesundheit GmbH, Essen, Germany, which was sub-contracted by ZEG-Berlin. Beate Villinger is a consultant of AstraZeneca.

Ethical Approval. All patients who met inclusion criteria were included in the study. Use of the BKK database for health services research is fully compliant with German federal law; health insurance companies were informed of the project, and required approvals were received from BKK. The study conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. Informed consent by patients was not necessary and institutional review board/ethical approval

was not required, as these claims data are de-identified.

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