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ORIGINAL RESEARCH

Real-World Burden of Immunosuppressant-Treated Lupus Nephritis: A German Claims Database Analysis

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ABSTRACT

Introduction: This retrospective cohort study (GSK213737) aimed to characterize treatment patterns, healthcare resource utilization (HCRU), and costs in patients with lupus nephritis (LN) initiating immunosuppressant therapy in clinical practice in Germany, to better understand the full picture of the real-world burden of LN.

Methods: Adult patients with LN who initiated mycophenolate mofetil (MMF), intravenous cyclophosphamide (CYC), azathioprine (AZA), tacrolimus, cyclosporin A, or rituximab therapy in 2011–2017 (index therapy) were identified from the Betriebskrankenkassen German Sickness Fund database. Treatment patterns, including immunosuppressant discontinuations, and therapy switches, were assessed (maximum follow-up 4 years). Corticosteroid use, HCRU, and total economic costs were also evaluated. HCRU and costs were compared with matched controls (individuals without systemic lupus erythematosus [SLE]/LN matched by age, sex, and baseline Charlson Comorbidity Index).

Results: Among 334 patients with LN, the median (interquartile range) duration of index immunosuppressant therapy use was 380.5 (126, 1064) days. Of those patients with 4 years complete enrollment, 70.8% had ≥ 1 discontinuation and 28.8% switched therapy. While most patients (71.2%) received only one immunosuppressant, gaps in treatment were common. After 1 year of follow-up, 41.6% of patients had a prednisone-equivalent corticosteroid dose of ≥ 7.5 mg/day. Patients with LN had greater HCRU use for most categories assessed and increased mean total costs per person-year versus controls (€15,115.99 versus €4,081.88 in the first year of follow-up).

Conclusions: This real-world analysis demonstrated the considerable burden of immunosuppressant-treated LN in Germany, with a high rate of discontinuations, frequent use of high-dose corticosteroids, and substantial HCRU/costs.

Kerry Gairy was affiliated to Value Evidence and Outcomes, GSK at the time of the study.

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Key Summary Points

Lupus nephritis (LN), a common manifestation of systemic lupus erythematosus (SLE), is associated with substantial healthcare resource utilization (HCRU) and has an estimated prevalence of 15 per 100,000 in Germany.

The current complex treatment pathways for LN, and disease burden experienced by patients, require further understanding to improve outcomes with targeted new therapies; this real-world study characterized treatment patterns, HCRU, and costs in patients with active LN initiating immunosuppressant therapy using administrative claims data.

Most German patients with LN initiating immunosuppressants had ≥ 1 treatment discontinuation over the 4-year follow-up period, with a smaller proportion switching therapies; in addition, these patients received high doses of corticosteroids even after initiation of immunosuppressants.

There was considerable HCRU and economic burden seen in patients with LN compared with the non-SLE/LN control group: a higher proportion of patients with LN had hospitalizations, ambulant hospital visits, outpatient visits, outpatient prescriptions, and remedies and other benefits; costs were also higher across all years of follow-up, particularly in year 1 where costs were nearly four times higher in patients with LN compared with the control group.

Current treatment pathways for LN in Germany may not provide adequate disease management, necessitating more effective, well-tolerated treatments.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune, chronic inflammatory disease that affects multiple organs and tissues [1, 2]. Using claims data, the prevalence of SLE in Germany was estimated at 56 per 100,000 in 2014 [3]. Lupus nephritis (LN), a form of glomerulonephritis, is a common manifestation in patients with SLE [4], with an estimated prevalence in Germany of 15 per 100,000 in 2017 [5]. LN has a chronic disease course and is associated with reduced quality of life, organ damage accrual, and increased risk of end-stage kidney disease (ESKD) and death [4, 6].

Treatment goals for LN focus on preserving kidney function, preventing disease flares/relapses and organ/tissue damage, and managing comorbidities, to ultimately improve disease-related quality of life and reduce morbidity and mortality [7, 8]. Clinical guidelines recommend an initial induction phase of mycophenolate mofetil (MMF; or mycophenolic acid [MPA]) or cyclophosphamide (CYC) in combination with corticosteroids for the treatment of active class III or IV LN (with/without class V) [7–9]. A prolonged maintenance phase of MMF or azathioprine (AZA), with or without corticosteroids, is then recommended for patients who respond to induction therapy [7–9]. For patients who do not respond, a switch in induction therapy, and if this is unsuccessful, treatment with rituximab or adding a calcineurin inhibitor in combination with corticosteroids is recommended [7–9]. Immunosuppression in combination with corticosteroids is also recommended for patients with active class V LN and nephrotic syndrome [7, 8].

Corticosteroids are a cornerstone of treatment for SLE and LN because of their potent anti-inflammatory and immunosuppressive properties [7, 8, 10]. However, prolonged use of corticosteroids can be associated with multiple serious, long-term adverse effects and an increased risk of irreversible organ damage [11–13]. Immunosuppressants can also adversely affect several organ systems, as well as increasing the risk of infections [14–20]. Furthermore, current regimens have limited

efficacy in the treatment of LN; some patients fail to achieve complete renal remission, many experience relapses, and up to 28% progress to ESKD or death [14, 16, 21–24].

Current treatment pathways for LN are complex. Given the need to improve outcomes and the emergence of new therapies, an understanding of existing treatment patterns, disease burden, and management is important. Previously, a comprehensive review, mostly based on US claims data, defined the burden and healthcare resource utilization (HCRU) associated with LN as substantial [25]; however, data on real-world immunosuppressant treatment patterns in patients with LN, and associated costs and HCRU, are limited.

The aim of this study was to characterize treatment patterns, HCRU, and costs in real-world patients with active LN initiating immunosuppressant therapy, based on administrative claims data from the German Statutory Health Insurance (SHI) system. By assessing these data, we aim to define the real-world burden of LN.

METHODS

Study Design and Data Source

In this retrospective cohort study (GSK study 213737), adult patients with LN who initiated or switched to an immunosuppressant of interest (MMF, intravenous CYC, AZA, tacrolimus, cyclosporin A, or rituximab) in 2011–2017 were identified from 2010–2019 administrative claims data in the Betriebskrankenkassen (BKK) German Sickness Fund database. The BKK contains detailed longitudinal information on insured patients for all services refunded by the German SHI system and includes data on patient demographics, hospital information, and patient medical history, including diagnoses, prescriptions, and HCRU.

The index date was defined as the date of the initial immunosuppressant prescription fill (Supplementary Materials Figure S1), with no evidence that the patient received the initiated study medication in the previous 6 months (12 months in the case of rituximab; washout period) and provided they met all other inclusion/exclusion criteria; patients could be included if they switched immunosuppressants but otherwise met the criteria for inclusion/exclusion. Additionally, preceding the washout period, patients may have received other immunosuppressants, including the immunosuppressant of interest.

Patient eligibility and baseline characteristics were assessed in the year prior to, or the calendar year quarter including, the index date (the baseline period), and immunosuppressant/concurrent medication use was inferred from prescription claims. Follow-up data for patients after initiation of immunosuppressant therapy was assessed until administrative censoring, death, disenrollment, or a maximum follow-up of 4 years. In cases where the patient received multiple courses of immunosuppressant therapy during the data collection period, index date and classification of the immunosuppressant subgroup were based on the first eligible course of treatment (the index course).

For assessment of HCRU and economic costs, data for patients with LN initiating immunosuppressant therapy were compared with data from a matched control group. The control group consisted of insured individuals without SLE/LN across the entire database. Control individuals were matched to the patients with LN treated with immunosuppressants by age (within a 5-year age strata), sex, and baseline Charlson Comorbidity Index (CCI). Matching was conducted separately for each index year for patients with data for the entire year.

Study Population

Patients $\geq$ 18 years of age were eligible for inclusion if they were prescribed an immunosuppressant of interest between 2011 and 2017 and had a diagnosis of LN (defined as having $\geq$ 1 diagnostic code for SLE and $\geq$ 1 diagnostic code for renal disease according to the International Classification of Diseases 10th revision—German modification [ICD-10-GM] in the year preceding or in the same calendar year quarter as the index date [index quarter]).

Patients also had to be insured and have data available for 1 year prior to the index date.

Exclusion criteria comprised prescription of the initiated study drug during the washout period and/or simultaneous prescription of > 1 study medications on the index date (Supplementary Materials Figure S2). Patients with other indications (ICD-10-GM codes) for the study drug (including leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, ovarian and breast cancer, Ewing's sarcoma, small cell lung cancer, neuroblastoma, and organ transplantation, including pre-index date kidney transplantation) during the baseline assessment window or index quarter, and patients with drug-induced SLE, were also excluded.

Individuals eligible for the matched control population were ≥ 18 years of age, completely insured between 2010 and 2019, included in the BKK database, and had no ICD-10-GM codes for SLE.

All patient data in the database are anonymized to comply with German data protection regulations; therefore, informed consent and ethics committee or institutional review board approval were not required.

Study Outcomes

Primary outcomes were the duration of index immunosuppressant therapy (intravenous CYC, MMF, AZA, tacrolimus, cyclosporin A, or rituximab), the number of immunosuppressant therapies received, and the time to discontinuation or switching of immunosuppressant therapy. Discontinuations and switching of therapies were identified from outpatient pharmacy claims. Discontinuation of immunosuppressants was defined as any gap in immunosuppressant prescriptions of > 6 months (1 year in the case of rituximab). The discontinuation date was calculated from the date of the last prescription by adding the number of days the patient was hypothesized to be using an immunosuppressant plus an appropriate "allowed gap". Switching was defined as the date of the first prescription fill of an alternative drug during the follow-up period.

Secondary outcomes included the dose of oral corticosteroids received, HCRU (hospitalizations, ambulant hospital visits, outpatient visits, outpatient prescriptions, remedies and other benefits, work disability, and long-term work disability), and annual economic costs (total and by class of immunosuppressive therapy).

Analyses

All analyses were descriptive in nature (i.e., no hypothesis testing was conducted). For baseline characteristics, categorical variables are presented as percentages, continuous variables as the mean and standard deviation (SD).

The duration of index immunosuppressant therapy overall and by type was described as the median (interquartile range [IQR]). The number of unique therapies was reported for patients with LN with complete follow-up at year 1 and year 4. Data on treatment discontinuations and switches were reported for patients with LN with complete follow-up at 1-, 2-, 3-, or 4-year intervals, and cumulative incidence curves were constructed for the first discontinuation or therapy switch over years 1–4. For the cumulative incidence curves, death and switching were treated as competing risks in the discontinuation calculations, and death and discontinuation were treated as competing risks for the calculations of therapy switches. Sankey diagrams were developed for patients with LN with complete follow-up at 1-, 2-, 3-, or 4-year intervals, to allow visualization of the changes in immunosuppressant therapy, and included "discontinued treatment" as a line of treatment.

The mean cumulative oral corticosteroid dose (prednisone-equivalent) was estimated in the baseline period and year 1 using information from pharmacy claims; patients were also categorized by dose (≥ 5 mg/day, ≥ 7.5 mg/day, and ≥ 10 mg/day). Patients could be included in multiple categories where eligible. The mean prednisone-equivalent corticosteroid dose was calculated by dividing total corticosteroid dose on days when immunosuppressant was received by the number of days the immunosuppressant was received. For patients with prescription

claims extending before or after a time point used to define the start or end of a treatment interval, respectively, only the days of supply falling into the treated interval were included in the analysis.

HCRU and economic costs were assessed for patients with LN treated with immunosuppressants and control individuals without SLE/LN in the baseline period prior to index date and during 1, 2, and 3 years of follow-up after index date. Total annual economic costs were reported in Euros, adjusted to 2019 values (the last year available in the dataset).

Ethics

This article does not contain any studies with human participants or animals performed by any of the authors. Permission was granted for this specific use of the BKK German Sickness Fund database. All methods with respect to data acquisition/extraction/preparation/verification were performed in accordance with relevant guidelines and regulations. As this study utilized data that was de-identified and anonymized, it was deemed that the study did not require review/approval from an institutional review board or collection of informed consent.

RESULTS

Patients

The study cohort comprised 334 patients with LN who initiated immunosuppressant therapy between 2011 and 2017 (Supplementary Materials Figure S2). The index immunosuppressant therapy initiated was AZA for 150/334 (44.9%) patients, MMF for 121/334 (36.2%) patients, rituximab for 30/334 (9.0%) patients, and CYC for 22/334 (6.6%) patients. The seven and four patients who initiated cyclosporin A and tacrolimus, respectively, were combined in a subgroup for calcineurin inhibitors (11/334; 3.3%).

Most patients were female (n = 264, 79.0%) and the mean (SD) age was 48.4 (17.0) years (Table 1). The mean (SD) baseline CCI index for the patients was 3.1 (2.3). During the baseline period, 76.6% of patients received systemic corticosteroids; a subset of patients were previously on immunosuppressant(s) prior to initiating the index immunosuppressant, including AZA (16.8%) and MMF (13.8%). The most frequent extra-renal SLE manifestations were thrombosis (16.8%), vasculitis (16.5%), and neuropathy (15.0%).

Overall, of the 334 patients included, 266 were followed for 3 years and 219 were followed for 4 years. Reasons for loss to follow-up included reaching the end of the study period (n = 256, 76.6%), death (n = 39, 11.7%), and end of continuous enrollment (n = 39, 11.7%).

Treatment Patterns

The median (IQR) duration of the index immunosuppressant therapy in all patients with LN was 380.5 (126, 1064 days and appeared to be longest for MMF (683.0 [255.0, 1088.0] days, n = 121) and shortest for CYC (75.5 [49.0, 119.0] days, n = 22). The median (IQR) duration of therapy with AZA was 368.0 (154.0, 1182.0) days (n = 150) (Supplementary Materials Table S1).

The most common reason for the end of the index immunosuppressant therapy episode was discontinuation (n = 173, 51.8%), followed by being censored by the end of follow-up (n = 89, 26.6%), switching treatments (n = 64, 19.2%), and death (n = 8, 2.4%).

Among patients with LN who had a full year of follow-up after the index date, most (266/319, 83.4%) received one (the index) immunosuppressant therapy. Among patients with 4 years of follow-up, 156/219 (71.2%) of patients received one immunosuppressant therapy, 43/219 (19.6%) received two immunosuppressants, and 15/219 (6.8%) and 5/219 (2.3%) received three and four immunosuppressants, respectively. The mean (SD) number of immunosuppressant therapies during the 4 years was 1.4 (0.7); patients receiving CYC or rituximab as index treatment had the highest mean (SD) number of therapies (2.5 [0.8] and 1.7 [1.0], respectively).

Overall, the proportion of patients with LN who initiated immunosuppressant therapy and

Table 1 Baseline demographics and disease characteristics[a]

	Overall patients (N = 334)
Age in years, mean (SD)	48.4 (17.0)
Female, *n* (%)	264 (79.0)
Medications[b], *n* (%)	
Systemic corticosteroids	256 (76.6)
ACE inhibitor, ARB	184 (55.1)
Antimalarials	130 (38.9)
AZA	56 (16.8)
MMF	46 (13.8)
Methotrexate	28 (8.4)
Cyclosporin A	10 (3.0)
CYC	6 (1.8)
Rituximab	5 (1.5)
Belimumab	5 (1.5)
Leflunomide	5 (1.5)
SLE manifestations, *n* (%)	
Moderate[c]	
Vasculitis	55 (16.5)
Neuropathy	50 (15.0)
Pleurisy	24 (7.2)
Enteritis	23 (6.9)
Severe[c]	
Thrombosis	56 (16.8)
Stroke TIA	31 (9.3)
Acute confusional state	12 (3.6)
Cranial neuropathy	10 (3.0)
Renal manifestations[d], *n* (%)	
Renal other	188 (56.3)
Nephritis	165 (49.4)
Dialysis/ESKD	11 (3.3)
CCI, mean (SD)	3.1 (2.3)

[a]Baseline age was determined at index date; the baseline assessment window for prescriptions included the four quarters preceding the index quarter and the pre-index part of the index quarter; the baseline assessment window for outpatient diagnoses included the four quarters preceding the index quarter; [b]patients were required to have no evidence of having received the index immunosuppressant therapy in a 6-month washout window (extended to 12 months for rituximab), but could have received other immunosuppressants; [c]four most commonly reported manifestations; [d]three most commonly reported manifestations

ACE angiotensin-converting enzyme; *ARB* angiotensin receptor blockers; *AZA* azathioprine; *CCI* Charlson Comorbidity Index; *CYC* cyclophosphamide; *ESKD* end-stage kidney disease; *MMF* mycophenolate mofetil; *SD* standard deviation; *SLE* systemic lupus erythematosus; *TIA* transient ischemic attack

had ≥ 1 treatment discontinuation appeared to increase during the 4-year follow-up period (40.4% [129/319] of patients with at least 1 year of follow-up; 70.8% [155/219] of patients with 4 years of complete enrollment) (Table 2). The proportion of patients with any treatment switches appeared to increase during follow-up, though most patients initiating immunosuppressants did not switch therapies (71.2% [156/219] of patients with 4 years of complete enrollment did not switch therapies) (Table 2).

When using time-to-event methods to describe time to discontinuation among patients with LN by the index immunosuppressant, patients receiving AZA, MMF, a calcineurin inhibitor, or rituximab appeared to have a higher risk of first discontinuation compared with patients receiving index CYC (Fig. 1a). However, this may have been driven by the high amount of switching among patients initiating CYC, which was a competing risk when quantifying time to discontinuation

Table 2 Number and proportion of patients with treatment discontinuations and treatment switches during 1, 2, 3, and 4 years of follow-up among those with the corresponding years of complete enrollment

	Year 1 (*N* = 319)		**Year 2 (*N* = 307)**		**Year 3 (*N* = 266)**		**Year 4 (*N* = 219)**	
Total number of discontinuations[a]	*n*	%	*n*	%	*n*	%	*n*	%
0	190	59.6	144	46.9	97	36.5	64	29.2
1	117	36.7	124	40.4	110	41.4	93	42.5
2	12	3.8	29	9.4	42	15.8	45	20.5
3			10	3.3	11	4.1	8	3.7
4					5	1.9	4	1.8
5					1	0.4	4	1.8
6							1	0.5
Total number of switches[b]								
0	268	84.0	240	78.2	202	75.9	156	71.2
1	40	12.5	49	16.0	43	16.2	36	16.4
2	8	2.5	10	3.3	9	3.4	13	5.9
3	3	0.9	6	2.0	10	3.8	11	5.0
4			2	0.7	2	0.8	3	1.4

[a]Discontinuations were defined as any gap in immunosuppressant prescriptions of > 6 months, or for rituximab any gap of > 1 year. Patients could be eligible for inclusion in both categories, since they could switch treatments before discontinuation; [b]switch events were recorded based on prescriptions for alternative immunosuppressant regimens and included switches from monotherapy to combination and switches from combination to monotherapy with the same drug

(Fig. 1b). Except for CYC, discontinuation appeared to be more common than switching across the different index immunosuppressants.

The complex and varied patient treatment pathways over the 4 years of follow-up are shown in Fig. 2 and Supplementary Materials Figure S3. Most patients with LN received one (the index) immunosuppressant therapy; however, breaks in treatment were common and a small number of patients with LN switched immunosuppressant therapies multiple times.

Oral Corticosteroid Use

During the baseline period, 75.4% (252/334) of patients with LN received oral corticosteroids with a mean cumulative prednisone-equivalent dose of 6.8 mg/day, which increased to 9.0 mg/day after year 1 follow-up. The proportion of patients with LN who received oral corticosteroids increased between baseline and year 1 across all dose categories (Table 3). After 1 year of follow up, 61.1% (204/334) of patients with LN had a prednisone-equivalent oral corticosteroid dose of ≥ 5.0 mg/day, 41.6% (139/334) had a dose of ≥ 7.5 mg/day, and 30.2% (101/334) had a dose of ≥ 10.0 mg/day.

HCRU and Economic Costs

For comparisons of HCRU and economic costs, the 334 patients with LN were matched to 1336 (4:1) non-SLE/LN controls in the BKK database (Supplementary Materials Figure S2). Non-SLE/LN controls were matched on sex, age (within 5-year strata), and CCI (mean [SD] score was

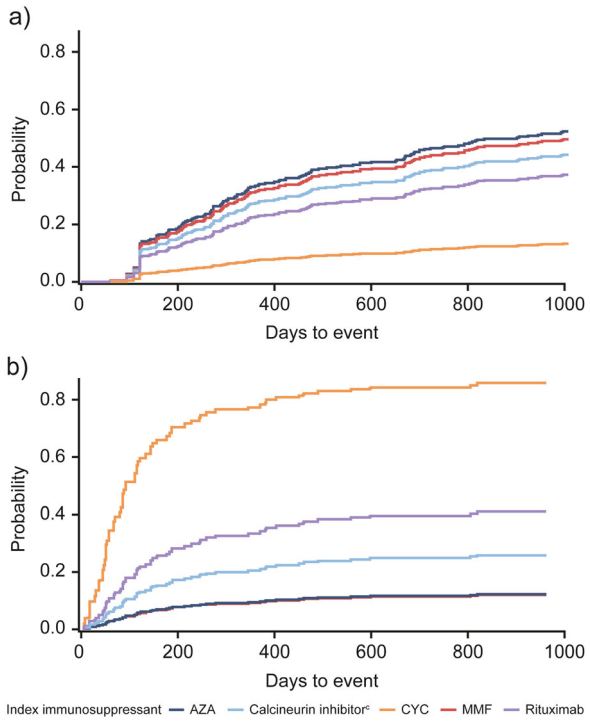

Fig. 1 Cumulative incidence of first discontinuation of index immunosuppressant therapy[a] (**a**) and first switch of index immunosuppressant therapy[b] (**b**) over 4 years of follow-up. [a]Considering switch and death as competing risks, discontinuation was defined as any gap in immunosuppressant prescriptions of > 6 months (1 year in the case of rituximab); [b]considering discontinuation and death as competing risks, switching was defined as the date of the first prescription fill of an alternative drug during the follow-up period; [c]includes tacrolimus. *AZA* azathioprine; *CYC* cyclophosphamide; *MMF* mycophenolate mofetil

3.1 [2.3] for both patients with LN and non-SLE/LN controls).

During follow-up, a higher proportion of patients with LN compared with non-SLE/LN controls had hospitalizations, ambulant hospital visits, outpatient visits, outpatient prescriptions, and remedies and other benefits (Fig. 3). For long-term work disability, HCRU was the same or greater in patients with LN versus non-SLE/LN controls at all time periods; however, the same trend was not observed for overall work disability. The largest differences in the proportions of patients with LN compared with non-SLE/LN controls in terms of HCRU were for hospitalizations and ambulant hospital visits; the proportion of patients hospitalized was over threefold higher for those with LN compared with non-SLE/LN controls in year 1 and over twofold higher in years 2 and 3. The length of hospital stays (in days per patient-year) was approximately sixfold greater in patients with LN versus non-SLE/LN controls in the baseline period and in year 1, and approximately three- and fivefold greater in years 2 and 3, respectively.

Hospital admission costs were the greatest contributors to total cost and were highest in year 1. In patients with LN, hospital admission costs accounted for 48.5, 35.2, and 37.2% of total costs in years 1, 2, and 3, respectively; for the matched controls, the contributions were 29.8, 28.1, and 23.5% for years 1, 2, and 3, respectively.

The annual total medical costs (mean [SD]) for patients with LN versus non-SLE/LN matched controls (Supplementary Materials Figure S4) were approximately 3.2-fold higher in the baseline period (€12,815.55 [€20,230.59] vs. €4026.30 [€8193.21]), 3.7-fold higher in year 1 (€15,115.99 [€21,097.15] vs. €4081.88 [€10,729.14]), and approximately threefold higher in years 2 and 3 (€11,898.93 [€16,363.84] vs. €3983.38 [€7993.27] and €11,551.42 [€17,483.32] vs. €3773.60 [€8452.49], respectively). For the baseline period and across all years of follow-up, costs (mean [SD]) were highest among patients with LN who received rituximab as index treatment (e.g., at year 1: €31,662.46 [€40,074.23]) followed by CYC (e.g., at year 1: €21,405.18 [€22,467.85]) (Supplementary Materials Figure S4).

DISCUSSION

This real-world study in Germany highlighted the complexity of treating patients with LN and the need for alternative, effective treatment regimens that adequately control LN. Over the follow-up period, most patients discontinued immunosuppressant treatment, some switched therapies, and many received high doses of oral corticosteroids. Furthermore, the management of these patients was associated with substantial HCRU and economic burden.

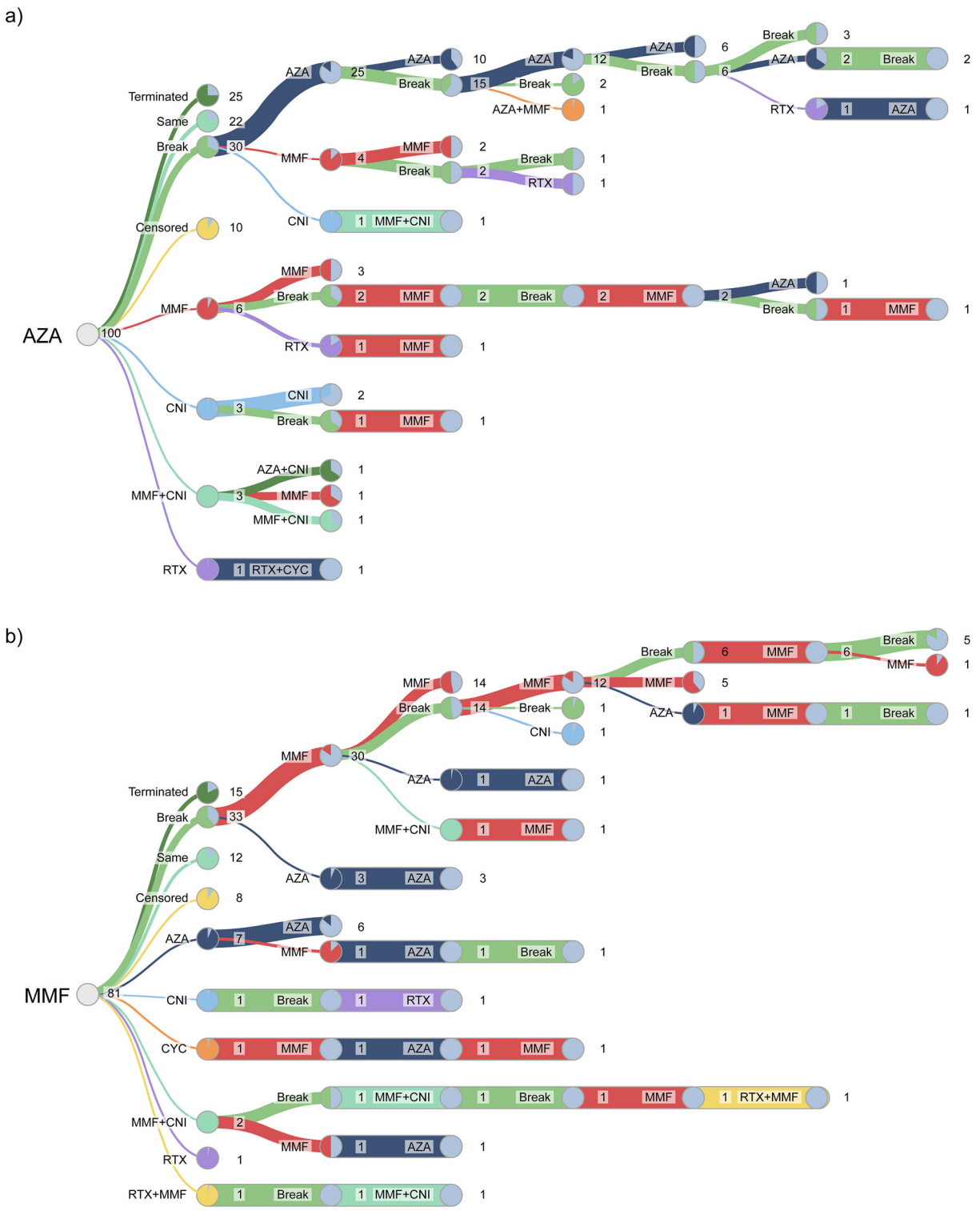

Fig. 2 Immunosuppressant treatment pathways over 4 years for AZA (N = 100) (**a**) and MMF (N = 81) (**b**). *Circles* represent the points of pathway branching, *width of bars* is representative of the proportion of patients on that treatment pathway. *AZA* azathioprine; *CNI* calcineurin inhibitor; *CYC* cyclophosphamide; *MMF* mycophenolate mofetil; *RTX* rituximab

Table 3 Proportion of patients receiving oral corticosteroids at baseline and year 1, categorized by prednisone-equivalent dose ($N = 334$)

Prednisone-equivalent dose (mg/day)	Proportion of patients with steroid use at baseline, *n* (%)	Proportion of patients with steroid use at year 1 follow-up, *n* (%)
Any dose	252 (75.4)	287 (85.9)
≥ 5.0	134 (40.1)	204 (61.1)
≥ 7.5	85 (25.4)	139 (41.6)
≥ 10.0	58 (17.4)	101 (30.2)

Treatment Patterns

The duration of index therapy was longest for MMF and shortest for CYC, as expected given that MMF is recommended as both induction and maintenance therapy while CYC is recommended for 3–6 months induction therapy before a switch to maintenance therapy [7–9]. However, of patients with 4 years of complete enrollment, 70.8% of patients with LN had ≥ 1 discontinuation of immunosuppressant therapy and "breaks" in therapy were common. Reasons for discontinuation and "breaks" in therapy are not captured in administrative claims data and therefore could not be explored, but merit further investigation since a lack of efficacy, tolerability concerns, and non-adherence to treatment seem likely to play a role.

Although most patients received only one immunosuppressant over the follow-up period, almost 10% received three or four different immunosuppressant therapies, suggesting poor renal responses and/or tolerability issues with multiple treatments in this subgroup. The numbers of different immunosuppressants received and treatment switches were notably higher in patients initiating CYC and, to a lesser extent, rituximab compared with patients initiating other therapies. This likely reflects the more common use of these drugs as induction

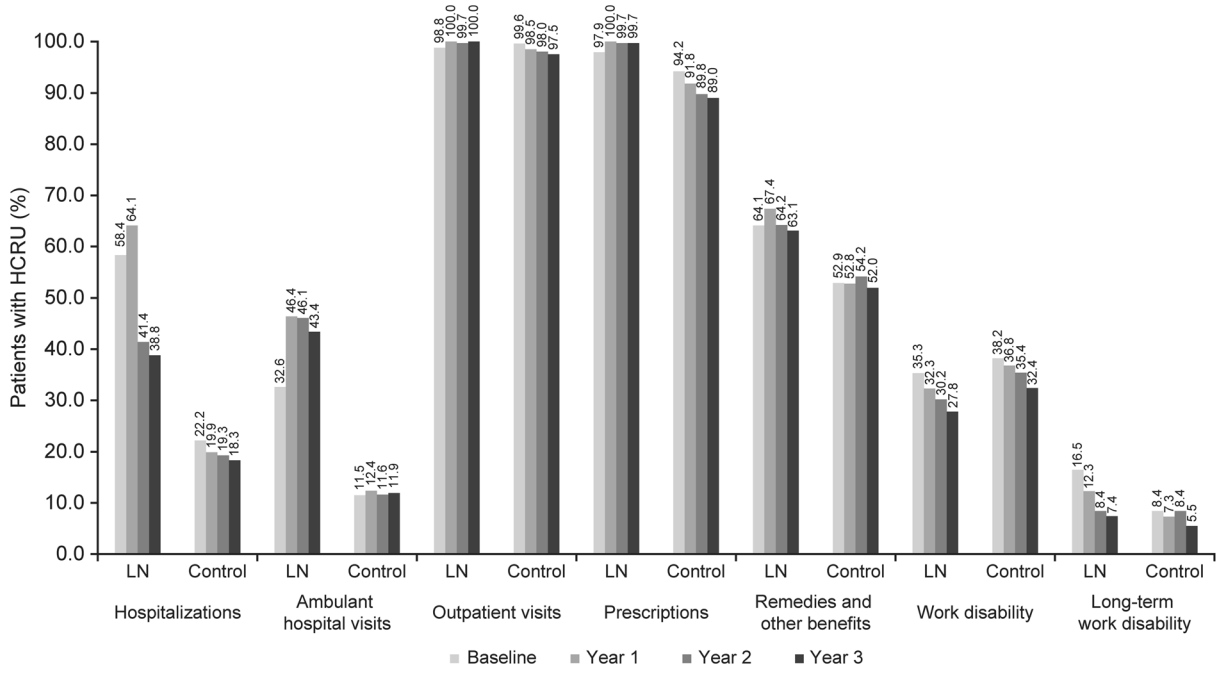

Fig. 3 HCRU in patients with LN compared with control individuals with no SLE/LN at baseline and over 1, 2, and 3 years of follow-up. Baseline: LN, $N = 334$; control, $N = 1336$. Year 1: LN, $N = 334$ LN; control, $N = 1336$. Year 2: LN, $N = 321$; control, $N = 1284$. Year 3: LN, $N = 309$; control, $N = 1236$. *HCRU*, healthcare resource utilization; *LN*, lupus nephritis; *SLE* systemic lupus erythematosus

rather than maintenance therapies, and possible reservation for patients with more severe or refractory nephritis, who may be more likely to have poor renal responses necessitating treatment switches. However, these analyses are descriptive and the reasons behind therapy changes are speculative and in need of further study.

Oral Corticosteroid Use

Most patients were receiving oral corticosteroids at baseline, and the proportion increased slightly in the first year after initiation of immunosuppressant therapy. SLE management guidelines recommend maintaining average prednisone-equivalent corticosteroid doses $\leq$ 7.5 mg/day [7, 8]. In this study, the mean prednisone-equivalent corticosteroid dose was 9.0 mg/day, and almost a third of patients received a dose of $\geq$ 10.0 mg/day in the year following immunosuppressant initiation. Multiple reasons may underly the frequent use of high doses of corticosteroids at baseline and during follow-up, including the need for disease activity control before the onset of immunosuppressant treatment and/or during discontinuations/"breaks" over 1 year of follow-up and the limited efficacy of immunosuppressant therapies. The observed use of high-dose corticosteroids, beyond guideline levels, highlights an unmet need for effective corticosteroid-sparing treatment options; however, more detailed and differentiated analysis of treatment patterns and pre-index therapy would be needed to describe long-term corticosteroid prescribing after the initiation of immunosuppressants in real-world settings.

HCRU and Economic Cost

Across the 3 years of follow-up, the proportion of patients with HCRU was greater among patients with LN versus non-SLE/LN controls for most categories assessed. These results are consistent with those from a German claims-based study of the burden of SLE, which showed higher rates of hospitalizations, hospital visits, prescriptions, and outpatient/ambulatory benefits among patients with SLE compared with matched controls [3]. The demonstration of substantial HCRU in immunosuppressant-treated patients with LN versus non-SLE/LN controls in the present German population adds to evidence from previous, mostly US-based, studies demonstrating high HCRU associated with LN compared with non-SLE controls or patients with SLE without renal manifestations [25].

The greatest difference in HCRU between the LN and control groups was for the rate of hospitalizations, which in year 1 was > 3-fold greater in patients with LN. Hospitalizations were also the greatest contributor to total cost in both groups; they were responsible for almost half of total costs in year 1 and over a third of costs in years 2 and 3 for patients with LN. These findings are similar to those from a US study, in which hospital/inpatient costs were the primary contributor and represented 36% of the total all-cause annual healthcare cost for a broad population of patients with LN [26]. A German study on the burden of SLE and organ damage also found that hospital admissions represented the greatest proportion of total annual costs in patients with SLE, accounting for 43.0% in year 1 [27].

The annual total medical costs were almost four times higher in patients with LN compared with non-SLE/LN controls in year 1 from the economic perspective of the third-party payer (i.e., the statutory health fund). These costs remained higher in years 2 and 3, consolidating previous reports of the economic burden of LN based on studies of generally broader, typically US-based patient populations [25]. Another US claims-based study noted that patients with LN had higher all-cause healthcare costs than a matched control group comprised of patients with SLE/without LN [28], consistent with earlier research [29–31]. In the previous study of SLE and organ damage in Germany, the total annual cost per person-year was more than twofold greater in patients with SLE with organ damage versus patients without organ damage in the first follow-up year, increasing over time to a difference of 3.2-fold in year 6 [32]. ESKD and dialysis have been shown to be significant drivers of costs associated with SLE/LN [25, 33],

patients with active LN and ESKD have higher medical costs versus patients with low disease activity [34]. In the current study, 3.3% of patients had ESKD/dialysis at baseline; therefore, HCRU and the economic burden of LN may be even greater in populations with a higher prevalence of ESKD/dialysis. When examining the costs according to index treatment received, the greatest costs over the 3 years of follow-up were for patients initiating rituximab or CYC; a contributory factor may be the use of these therapies in patients with more severe or refractory nephritis. Overall, the increased costs in patients with LN compared with the non-SLE/LN control group further illustrates the need for more effective treatment, to reduce this economic burden.

Limitations

The BKK database allows a novel insight into real-world treatment patterns, though due to the nature of the database, information is limited to patients with SHI. However, around 90% of the German population are covered by SHI, lessening the impact of this limitation. The BKK database does not include detailed information on certain patient demographics (e.g., social status, ethnicity, and income) or in-depth clinical data (e.g., laboratory results and imaging procedures to confirm the histological classification of LN). This is a common limitation of studies using administrative and claims data that precluded provision of the level of detail that may be available in other real-world data sources (e.g., disease-specific registries) and may have introduced measurement error based on data coding limitations or data entry error. When possible, efforts were made to reduce measurement error by using definitions from prior research and/or validation studies, such as when defining LN [26, 35]. Further, the BKK pharmacy claim records did not contain information on a patient's adherence to their prescribed medication, medications administered in hospitals, or intended use of prescribed medications (including to differentiate induction versus maintenance immunosuppressant therapy, as well as intended daily dose and length of therapy). Assumptions about how prescribed medications were used in practice were required, which is consistent with other studies using pharmacy claims to evaluate drug utilization patterns in real-world settings [36]. Lastly, for the HCRU and costs analyses, unmeasured confounding cannot be ruled out as a potential driver of the differences observed between LN and non-SLE/LN matched controls.

CONCLUSIONS

This study demonstrates that most German patients with LN initiating immunosuppressants discontinued therapy over the course of 4 years, with a smaller proportion switching therapies. These patients also received high doses of oral corticosteroids, with doses increasing after immunosuppressant initiation. Frequent discontinuations and therapy "breaks", most likely driven by limited efficacy, tolerability concerns, and/or issues with patient non-adherence with current treatments, may cause a worsening of disease and contribute to the considerable HCRU and economic burden observed in immunosuppressant-treated patients with LN compared with non-SLE/LN controls. Together, these findings suggest that current therapies do not adequately control LN, highlighting the need for more effective, well tolerated, and corticosteroid-sparing treatments.

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Data Availability. To request access to documents for this study, please submit an enquiry via https://www.gsk-studyregister.com/en/.

Declarations

Conflict of Interest. Elena Garal-Pantaler is an employee of Team Gesundheit GmbH. Michael Schultze and Marc Pignot are employees of ZEG – Berlin Center for Epidemiology and Health Research GmbH, which was contracted by GSK to conduct this study. Mary Elizabeth Georgiou and Jacob N Hunnicutt are employees of GSK and hold stocks and shares in the company. Kerry Gairy was an employee of GSK at the time this study was conducted and holds stocks and shares in the company (current affiliation: AstraZeneca, Global Market Access and Pricing, Cambridge, UK).

Ethical Approval. This article does not contain any studies with human participants or animals performed by any of the authors. Permission was granted for this specific use of the Betriebskrankenkassen German Sickness Fund database. All methods with respect to data acquisition/extraction/preparation/verification were performed in accordance with relevant guidelines and regulations. As this study utilized data that was de-identified and anonymized, it was deemed that the study did not require review/approval from an institutional review board or collection of informed consent.

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