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ORIGINAL RESEARCH

Treatment Patterns and Healthcare Resource Utilization Among Patients with Atopic Dermatitis: A Retrospective Cohort Study Using German Health Claims Data

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a common inflammatory skin disease. Many patients are initiating a systemic therapy, if the disease is not adequately controlled with topical treatment only. Currently, there is little real-world evidence on the AD-related medical care situation in Germany. This study analyzed patient characteristics, treatment patterns, healthcare resource utilization and costs associated with systemically treated AD for the German healthcare system.

Methods: In this descriptive, retrospective cohort study, aggregated anonymized German health claims data from the InGef research database were used. Within a representative sample of four million insured individuals, patients with AD and systemic drug therapy initiation (SDTI) in the index year 2017 were identified and included into the study cohort. Systemic drug therapy included dupilumab, systemic corticosteroids (SCS) and systemic immunosuppressants (SIS). Patients were observed for one year starting from the date of SDTI in 2017.

Results: 9975 patients were included (57.8% female, mean age 39.6 years [SD 25.5]). In the one-year observation period, the most common systemic drug therapy was SCS (> 99.0%). Administrations of dupilumab (0.3%) or dispensations of SIS were rare (cyclosporine: 0.5%, azathioprine: 0.6%, methotrexate: 0.1%). Median treatment duration of SCS, cyclosporine and

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azathioprine was 27 days, 102 days, and 109 days, respectively. 2.8% of the patients received phototherapy; 41.6% used topical corticosteroids and/or topical calcineurin inhibitor. Average annual costs for medications amounted to € 1237 per patient. Outpatient services were used by 99.6% with associated mean annual costs of € 943; 25.4% had at least one hospitalization (mean annual costs: € 5836). 5.3% of adult patients received sickness benefits with associated mean annual costs of € 5026.

Conclusions: Despite unfavorable risk–benefit profile, this study demonstrated a common treatment with SCS, whereas other systemic drug therapy options were rarely used. Furthermore, the results suggest a substantial economic burden for patients with AD and SDTI.

Keywords: Claims data analysis; Corticosteroids; Costs; Dermatitis; Atopic; Germany; Healthcare resource utilization

Key Summary Points

Why carry out this study?

Patients with atopic dermatitis (AD) who are more severely affected and who cannot manage their disease with topical anti-inflammatory drugs require systemic therapy.

Treatment patterns of systemic drug use (systemic corticosteroids, systemic immunosuppressants, and dupilumab), healthcare resource utilization and associated costs in patients with AD and systemic drug therapy initiation (aged $\geq$ 2 years) have not sufficiently been investigated under routine care conditions in Germany.

What was learned from this study?

Despite unfavorable risk–benefit profile, treatment with systemic corticosteroids was common (even in non-adults), whereas other systemic drug therapy options were rarely used.

Considering the observed treatment duration within this study, the use of systemic corticosteroids in most cases was no longer in line with European guideline recommendations.

AD treated with systemic drugs resulted in substantial direct (€ 3677 per patient per year) and indirect costs due to AD (€ 6235 per adult patient per year) in Germany.

INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by pruritus, eczematous lesions, and its chronically relapsing course. For European countries, a prevalence of 4.4% was estimated among adults based on survey data from 2016 [1]. In Germany, approximately 13% of children and adolescents aged 0–17 years are at least temporarily affected by AD [2]. Patients with AD often suffer from other allergic diseases, such as bronchial asthma and allergic rhinitis [3, 4], as well as psychological disorders, particularly depression [5–7]. The disease presents clinically in heterogeneous ways and is characterized by an alternating occurrence of acute flares followed by mild intervals [8]. If inadequately controlled, AD can lead to a reduced health-related quality of life in adults and children [6, 9].

Adequate disease control can be achieved by using disease activity-adapted treatment options in a step-wise manner according to the individuals' disease severity level (mild, moderate, and severe). Therapy options can be categorized into continuous and intermittent therapy. European guidelines recommend long-term non-pharmacological topical treatments (e.g., emollients and baths) as basic therapy and the avoidance of provocative factors [10].

Topical anti-inflammatory drugs such as topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI) can be used temporarily or, according to current guideline recommendations, as proactive treatment depending on the disease severity [10]. For patients more severely affected and suffering from frequent flares,

treatment can be intensified by using phototherapy (recommended for adults only), systemic immunosuppressive agents (SIS) such as cyclosporine (in-label), or systemic corticosteroids (SCS). The use of SCS can be considered in the treatment of acute flares or in conjunction with a therapy concept for the subsequent treatment in patients with severe disease progression according to current German and European guideline recommendations [11, 12]. The SIS, azathioprine, mycophenolate mofetil, and methotrexate (MTX), can be used as an off-label treatment in patients with severe AD [11]. Cyclosporine, off-label products, and SIS are only suitable for limited time intervals. One suitable long-term treatment option is the monoclonal antibody dupilumab, for which various studies have confirmed a favorable safety profile across all age groups, including children from the age of 6 years and elderly patients [13–17]. Dupilumab is approved and fully reimbursed for the treatment of moderate-severe AD in adults and adolescents aged 12 years and older, who are not adequately controlled with a single use of topical medications, since September 2017 [11, 12]. Since November 2020, it has also been approved for the treatment of severe AD in children aged 6–11 years. With baricitinib, tralokinumab, upadacitinib and abrocitinib, further systemic drug therapy options have been approved for the treatment of moderate-severe AD in adults in Germany since October 2020, June 2021, August 2021 and December 2021.

Several studies were published on the costs of AD in Germany [18–24]. Some of them reported direct and indirect costs for both children and adults [21, 23]. The most recent study was published in 2005 and found average annual total costs of € 1425 per patient (both children and adults) with AD [21]. As the medical care situation in AD has changed since then, more recent data on the costs of AD are needed.

Currently, there are few studies investigating the recent medical care situation and resource utilization of patients with AD undergoing systemic drug therapy in the German healthcare context. This study aims to (1) characterize patients with AD and systemic drug therapy initiation (SDTI) regarding their demographics and diagnosed comorbidities and (2) to describe current treatment patterns, (3) healthcare resource utilization (HCRU), and associated costs in this patient population.

METHODS

Data source

The data source of the present study was the InGef (Institute for Applied Health Research Berlin) research database. The anonymized database contains longitudinal claims data from approximately seven million individuals who are insured with one of more than 58 German statutory health insurance (SHI) companies included in this database. For the purpose of this analysis, an aggregated anonymized sample of approximately four million insured persons was used which can be considered representative of the German population regarding age and sex [25]. The InGef research database includes sociodemographic information such as sex, age, and region of residence. In addition, detailed information on hospitalizations, outpatient physician contacts and outpatient drug prescriptions can be obtained from the database. Inpatient data comprises the date of admission, date of discharge, the reason for discharge, diagnostic and therapeutic information with exact dates, and diagnoses. Diagnoses can be differentiated between hospital main discharge diagnoses and secondary diagnoses. Outpatient data also includes diagnostic and therapeutic information with exact dates. Inpatient and outpatient diagnoses are recorded through the coding according to the German Modification of the International Classification of Diseases, 10th Revision (ICD-10-GM). Outpatient prescription data of reimbursed drugs includes information on the date of prescription and dispensation as well as the pharmaceutical reference number. Based on a pharmaceutical reference database, information on the Anatomical Therapeutical Chemical code (ATC code), the defined daily dose (DDD), the packaging size, as well as the strength and formulation of the drug can be linked for each prescribed drug.

Since all patient-level data in the database are anonymized to comply with German data

protections regulations and German federal law, approval of an Ethics Committee was not required. The research was conducted in accordance with the Declaration of Helsinki.

Study design

A retrospective cohort study was conducted based on German claims data from January 01, 2016 until December 31, 2018. Patients with a documented AD diagnosis were included into the study cohort if they had SDTI between January 01, 2017 and December 31, 2017 (index period). SDTI was defined as the first documented health claim for systemic medication during the index period (index date) after a baseline period of 1 year without a respective claim. An observation period of 1 year after the index was used to assess the research question.

The study was of descriptive nature only; thus, no hypotheses were specified in advance and no sample size calculation was carried out.

Inclusion and exclusion criteria

Insured individuals were included into the study cohort, if they fulfilled all of the following criteria:

1. They were at least 2 years old at the end of the index period.
2. They had at least one documented diagnosis (hospital discharge diagnosis or confirmed outpatient diagnosis) of AD (ICD-10-GM: L20.8, L20.9) within the index period.
3. They had at least one health claim for systemic drug therapy (i.e., dupilumab, SCS or SIS) during the index period. The index date was defined as the first observable outpatient dispensation or inpatient administration of at least one systemic drug (see Table S2 in the electronic supplementary material for details) between January 01, 2017 and December 31, 2017.
4. They were continuously insured during the baseline period.
5. They were continuously insured during the observation period or until death.
6. They had a documented AD diagnosis at the index date or during the baseline period.

Insured individuals were excluded from the cohort if they did not fulfill the aforementioned inclusion criteria. Furthermore, missing information on year of birth and sex led to an exclusion. Since the present analysis focused on patients with SDTI, patients with AD and a documented health claim for systemic drug therapy during the baseline period were excluded from the analysis.

Assessment of patient characteristics

Patient characteristics were assessed during the post-index observation period. Socio-demographic variables included age and sex. To ascertain the comorbidity burden, main or secondary inpatient discharge diagnoses, and confirmed outpatient diagnoses were taken into account. The documentation of one of these diagnosis types was sufficient for identification. To describe the general comorbidity burden, the Elixhauser Comorbidity Score (ECS) comprising 31 single diseases (see Table S1 in the electronic supplementary material for details) was used [26–28]. Furthermore, the specific comorbidity burden was evaluated by a data-driven approach identifying the top-10 most frequent comorbidities.

Assessment of treatment patterns

Information on systemic drug therapy, concomitant topical medication (TCS, TCI), and other AD-related medication (excl. systemic drugs) were identified based on outpatient drug dispensations and, in the case of dupilumab, on inpatient administered drugs. Systemic medication was evaluated at the index date and during the observation period; whereas the assessment of concomitant treatment with TCS and/or TCI was based on the observation period only.

The use of concomitant TCI and/or TCS was analyzed considering the following categories: “receiving TCS while not receiving TCI”, “receiving TCI while not receiving TCS”, “not

receiving TCS or TCI", and "receiving TCS and TCI". The latter category does not necessarily imply the simultaneous use of both drug classes. Patients in this category did only receive at least one dispensation of each drug class within the 1-year observation period.

The operationalization of other AD-related medication is listed in Table S4 (see electronic supplementary material).

Drug therapy was classified by three- or four-digit level of the ATC code; specific drugs were classified by seven-digit level of the ATC code (see Tables S2, S3, and S4 in the electronic supplementary material for details). In the case of dupilumab, the corresponding OPS (German procedure classification) code was included in addition to the ATC code. Furthermore, the prescribed defined daily doses (DDD) and accumulated costs (pharmacy retail price) during the observation period were ascertained.

The persistence of systemic drug therapy was analyzed based on treatment discontinuation and switching behavior. To calculate the range and to define the run-out date of a prescription of systemic drugs, the package size was multiplied by the active ingredient content per tablet or the unit of other application forms and divided by the DDD of the active ingredient. Discontinuation of therapy was defined as a gap of > 90 days between the run-out date of a systemic drug and any subsequent prescription for the respective drug therapy. If the drug therapy was discontinued, the run-out date of the last dispensation was defined as the date of discontinuation. Switching was determined if a dispensation of another systemic drug therapy was documented within the supply period of the initial systemic drug therapy or during the 90-day period after the run-out date of the systemic drug therapy.

Assessment of HCRU and associated costs

HCRU and associated costs were determined both overall as well as due to AD. All analyzes were based on the 1-year post-index observation period. Analysis of all-cause HCRU included: hospitalizations, outpatient physician contacts, overall prescription medication, and sick leave. Assessment of HCRU due to AD included: hospitalizations due to AD (main discharge diagnosis of AD), outpatient phototherapy, AD-related medication, and sick leave due to AD.

At least one health claim of a respective service was sufficient to meet the criterion. For each healthcare service, relative frequencies and the mean number of utilized services were ascertained. Concerning hospitalizations and sick leave, mean duration was also assessed.

Total costs to the SHI and mean annual costs per patient were calculated for the respective healthcare service. All-cause direct costs comprised the following categories: outpatient costs, hospitalization costs, and overall prescription medication costs. Direct costs due to AD included outpatient phototherapy costs, costs for hospitalizations due to AD, and AD-related prescription medication costs. All-cause indirect costs and indirect costs due to AD were evaluated based on costs for sickness benefits (all-cause) and sickness benefits due to AD, respectively.

Health services that are paid for privately, such as over-the-counter (OTC) drugs, are not included in German claims data. Since OTC medication was not comprised in the database, associated out-of-pocket costs could not be analyzed.

Statistical analyses

The age was categorized into clinically relevant categories: 2–11 years, 12–17 years, and ≥ 18 years. Furthermore, the ECS was categorized into the following categories: 0 diseases, 1 disease, 2 diseases, 3 diseases, 4 diseases, 5 diseases, and ≥ 6 diseases.

Patient characteristics were stratified by sex, with comorbidities also stratified by age. Analyses concerning treatment patterns, HCRU and associated costs were carried out stratified by age. For categorical variables, frequencies and percentages were ascertained. For continuous variables, means, standard deviations (SD), and medians were calculated.

The proportion of patients with a specific comorbidity, use of medication or healthcare service was calculated by dividing the number

of patients fulfilling the respective criteria by the number of patients in the study cohort.

Mean annual costs of healthcare services were calculated by dividing the sum of costs by the number of patients receiving the respective health service during the observation period. Costs were analyzed descriptively. A more comprehensive analysis of the economic burden of the disease was not subject of this study.

Persistence of the index systemic drug therapy was described using Kaplan–Meier rates. The defined outcome was discontinuation of index systemic drug therapy. Treatment discontinuation was analyzed in days, based on the duration of treatment from the start date to the date of discontinuation or until the end of the 1-year observation period. Patients with no observed discontinuation of index systemic drug therapy or an ending of the insurance period during the obseravtion period were censored. The Kaplan Meier analysis was carried out separately for each drug/drug class as well as for the overall patient cohort.

All statistical analyses were of descriptive nature only. Data management and analyses were performed with the statistical software R (Version: Microsoft R Open 3.5.0).

RESULTS

Patient characteristics

Among the representative InGef sample in 2017 (n = 4,332,845), 3,940,142 insured individuals were continuously observable until the end of 2017 or until death. Of those, 3.7% had a prevalent AD diagnosis (n = 158,673). Of the latter, 10.6% received systemic medication (n = 16,548). Based on the aforementioned selection criteria, a total of 9975 patients with AD and SDTI were included in the study cohort (Fig. 1).

Patient characteristics are presented in Table 1. The mean age within the study cohort was 39.6 years (SD 25.5) with male patients having a lower mean age (34.8 years, SD 27.0) compared to female patients (43.0 years, SD 23.7). Females were slightly overrepresented in the study cohort (57.8%). 26.7% of the patients were under 18 years old with 22.5% and 4.2% being in the age of 2–11 and 12–17 years, respectively. 38.1% of the male patients were under 18 years of age, whereas only 18.3% of the female patients were younger than 18 years.

The mean number of diseases on the ECS was 2.3 (SD 2.5); 10.6% of the patients within the study cohort (female: 10.8%; male: 10.4%) showed at least 6 diseases. Females showed a higher general comorbidity burden in comparison with males. Overall, back pain (34.7%), acute upper respiratory infections (32.3%) and bronchial asthma (31.5%) were the most frequently observed comorbidities. Figure 2 depicts the most frequent comorbidities of the studied population stratified by age.

Treatment patterns of systemic drug use

The distribution of the index systemic drug therapy is depicted in Table S5 (see electronic supplementary material). At index, 99.0%, 0.4%, 0.3%, and 0.2% received dispensations of glucocorticoids, fixed-dose combinations of corticosteroids, cyclosporine and azathioprine, respectively. 0.1% of the patients received combined azathioprine and glucocorticoids. No cases, or fewer than five cases, were observed with dispensations of dupilumab, methotrexate, or other combinations.

In the observation period, SCS were the most frequently observed dispensed drugs. 99.2% of the patients received at least one dispensation of glucocorticoids and 0.5% at least one dispensation of fixed-dose combinations of corticosteroids (Table 2). Patients with dispensations of SIS such as cyclosporine (0.5%), azathioprine (0.6%) or methotrexate (0.1%) were rarely observed. Dupilumab was dispensed to a share of 0.3% of the patients. Stratifying by age, a similar distribution was observed and patients with dispensations of SCS were overrepresented in every age group.

As shown in Table 2, mean dispensed DDD of glucocorticoids were with 84.8 higher in the adult age group in comparison with younger age groups during the 1-year observation period (2–11 years: 10.0 mean DDD, 12–17 years: 45.2 mean DDD). In contrast, the intensity of

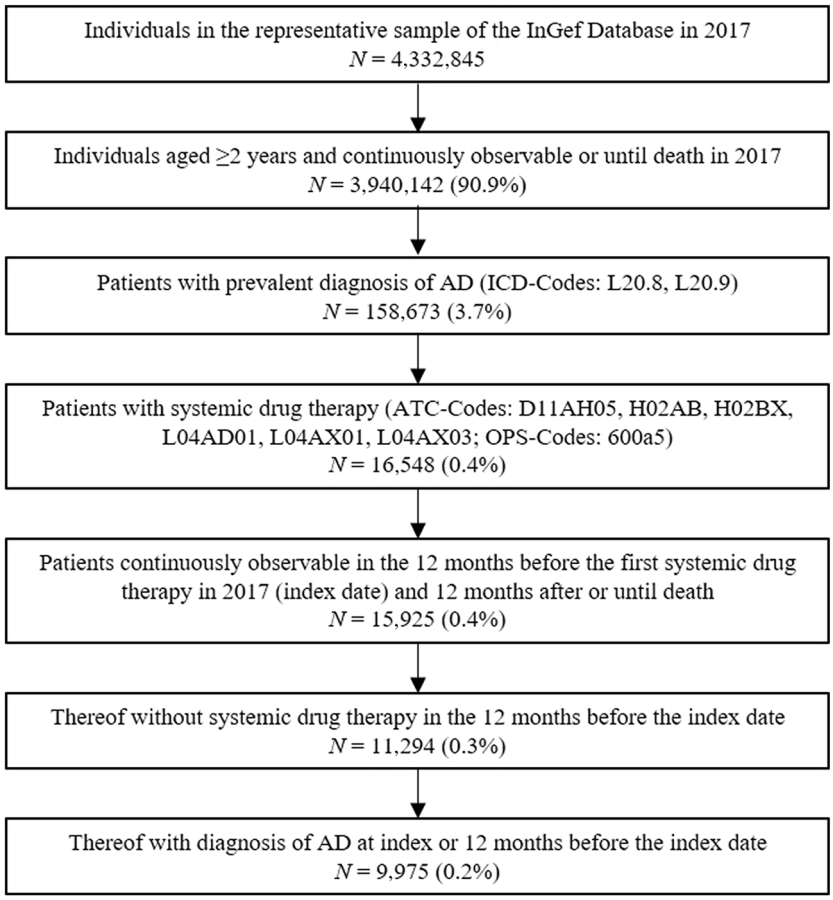

Fig. 1 Patient selection in year 2017. *AD* Atopic Dermatitis, *ICD* International Classification of Diseases, *ATC* Anatomical Therapeutical Chemical

systemic drug therapy with azathioprine was with 218.1 mean DDD higher in the age group of 12–17 years in comparison with the age group of ≥ 18 years (118.2 mean DDD).

A share of 2.8% of patients received at least one prescription for phototherapy. Prescriptions for phototherapy were observed within adult (3.8%) and non-adult patients (2–11 years: 0.0%, 12–17 years: 1.2%).

Persistence of systemic drug therapy

During the 1-year observation period, discontinuation of index systemic drug therapy was most frequent within patients treated with SCS (96.9%) followed by patients treated with SIS, such as cyclosporine (76.0%) and azathioprine (63.6%) (Table 3). Therapy with SCS lasted on average 46.3 days (SD 58.4) and with azathioprine 85.0 days (SD 85.6) whereas treatment with cyclosporine lasted on average 119.3 days (SD 104.4).

Figure 3 illustrates the time until discontinuation for each systemic treatment group. Overall (n = 9963), persistence was 35% and 19% after 45 days and 90 days. The subgroups differed substantially in size (SCS: n = 9912, cyclosporine: n = 25, azathioprine: n = 22). In the largest subgroup of patients treated with SCS, the probability of remaining under the index systemic treatment was 34% and 18% after 45 days and 90 days. After 1 week, the probability of being treated with SCS was 80%. Persistence in the cyclosporine subgroup was 76% and 52% after 45 days and 90 days, in the subgroup of patients treated with azathioprine

Table 1 Demographic characteristics and comorbidity of patients with AD and SDTI in the 1-year observation period

	Female (*n* = 5762)		**Male (*n* = 4213)**		**All (*n* = 9975)**	
	n	**%**	***n***	**%**	***n***	**%**
Age (years)						
2–11	846	14.7	1397	33.2	2243	22.5
12–17	210	3.6	207	4.9	417	4.2
18–29	695	12.1	373	8.9	1068	10.7
30–39	619	10.7	309	7.3	928	9.3
40–49	811	14.1	406	9.6	1217	12.2
50–59	1029	17.9	584	13.9	1613	16.2
60–69	755	13.1	407	9.7	1162	11.6
70–79	491	8.5	336	8.0	827	8.3
≥ 80	306	5.3	194	4.6	500	5.0
All	5762	100.0	4213	100.0	9975	100.0
Mean (SD)	43	23.7	34.8	27.0	39.6	25.5
Sex						
Female					5762	57.8
Male					4213	42.2
General comorbidity (ESC)						
0 diseases	1205	20.9	1183	28.1	2388	23.9
1 disease	1341	23.3	1281	30.4	2622	26.3
2 diseases	1065	18.5	565	13.4	1630	16.3
3 diseases	725	12.6	337	8.0	1062	10.6
4 diseases	477	8.3	226	5.4	703	7.0
5 diseases	327	5.7	183	4.3	510	5.1
≥ 6 diseases	622	10.8	438	10.4	1060	10.6
Mean (SD)	2.5 (2.5)		2.1 (2.5)		2.3 (2.5)	
Q1, Q3	1.0	3.0	0.0	3.0	1.0	3.0
Median	2.0		1.0		1.0	
Min, Max	0.0	19.0	0.0	18.0	0.0	19.0
Specific comorbidity (top 10)						
Back pain	2314	40.2	1149	27.3	3463	34.7
Acute upper respiratory infections	1754	30.4	1472	34.9	3226	32.3
Bronchial asthma	1822	31.6	1321	31.4	3143	31.5
Hypertension	1816	31.5	1197	28.4	3013	30.2

Table 1 continued

	Female (n = 5762)		Male (n = 4213)		All (n = 9975)	
	n	%	n	%	n	%
Vasomotor and allergic rhinitis	1727	30.0	1211	28.7	2938	29.5
Disorders of refraction and accommodation	1813	31.5	1116	26.5	2929	29.4
Other and unspecified dermatitis	1447	25.1	984	23.4	2431	24.4
Disorders of lipoprotein metabolism and other lipidemias	1282	22.2	848	20.1	2130	21.4
Somatoform disorders	1266	22.0	465	11.0	1731	17.4
Acute bronchitis	*	*	843	20.0	1670	16.7

ESC Elixhauser Comorbidity Score, *SD* standard deviation, *Q* quartile
*Not among the top 30 within this stratum

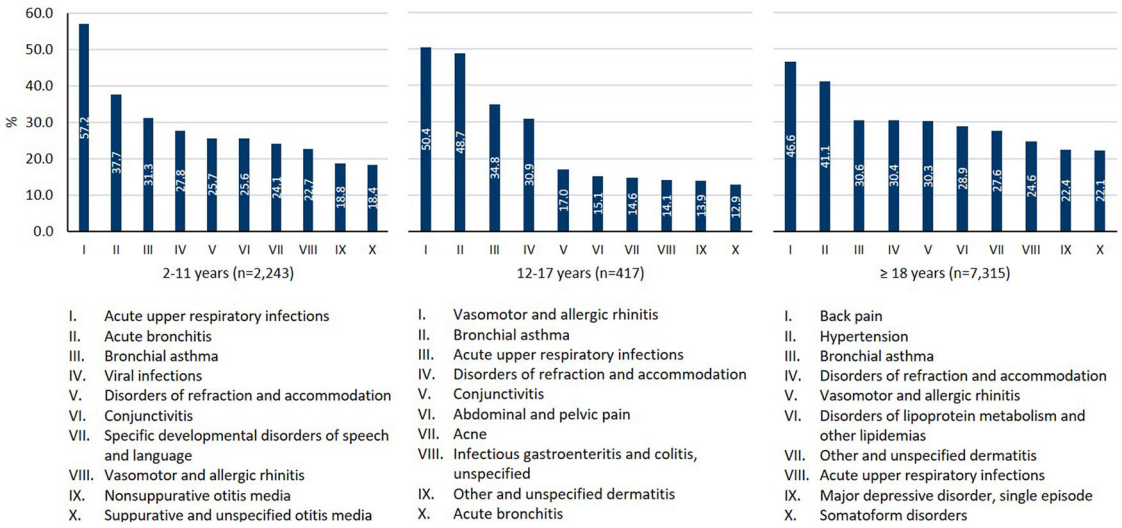

Fig. 2 Specific comorbidity (top 10), in the 1-year observation period, stratified by age

59% and 45% after 45 days and 90 days, respectively. Median treatment duration was 27 days in the SCS-subgroup, 102 days in the cyclosporine and 109 days in the azathioprine subgroup. Since none or fewer than five patients were identified initiating dupilumab or methotrexate treatment at the index, no data were available regarding treatment duration for this patient group.

Within the 1-year observation period, only a few switches could be observed. 51 patients (0.5%) were found to have switches to any other systemic drug therapy (Table 6).

Concomitant topical drug therapy (TCS and/or TCI)

58.4% of the patients neither received TCS nor TCI (Table 4). Within patients receiving dispensations of concomitant TCS and/or TCI, TCS was the most frequently dispensed drug class (34.5%). TCI was dispensed in 1.8% of the

Table 2 Use of systemic therapy (incl. phototherapy) during the 1-year observation period, stratified by age

	2–11 years (*n* = 2243)			12–17 years (*n* = 417)			≥ 18 years (*n* = 7315)			All (*n* = 9975)		
	n	%	Mean DDD	*n*	%	Mean DDD	*n*	%	Mean DDD	*n*	%	Mean DDD
Systemic drug therapy												
Glucocorticoids	2241	99.9	10.0	412	98.8	45.2	7245	99.0	84.8	9898	99.2	66.2
Azathioprine	5	0.2	83.3	6	1.4	218.1	49	0.7	118.2	60	0.6	125.3
Cyclosporine	< 5	–	–	< 5	–	–	45	0.6	95.1	51	0.5	93.9
Dupilumab	< 5	–	–	< 5	–	–	26	0.4	212.1	28	0.3	205.1
Methotrexate	–	–	–	< 5	–	–	< 5	–	–	5	0.1	72.0
Corticosteroids, fixed-dose combinations	–	–	–	–	–	–	45	0.6	19.4	45	0.5	19.4
*Phototherapy**	0	0.0		5	1.2		277	3.8		282	2.8	

Numbers which are too low or might allow indirect calculability of too low case numbers cannot be displayed due to data protection reasons
DDD defined daily dose, *SD* standard deviation,
*Including all patients, who received prescriptions for outpatient and inpatient phototherapy

Table 3 Time until discontinuation of index systemic drug therapy during the 1-year observation period (*n* = 9975), 90 days gap allowed

	n	Discontinuous users		Time to discontinuation	
		n	%	Mean	SD
Index systemic drug therapy					
Glucocorticoids, corticosteroids for systemic use	9912	9605	96.9	46.3	58.4
Cyclosporine	25	19	76.0	119.3	104.4
Azathioprine	22	14	63.6	85.0	85.6
Methotrexate	< 5	–	–	–	–
All	9963	9657	96.9	46.8	59.2

Numbers which are too low or might allow indirect calculability of too low case numbers cannot be displayed due to data protection reasons
SD standard deviation

patients; 5.3% received dispensations of both TCI and TCS.

Stratifying by age, dispensations of concomitant TCS treatment were more frequent in the adult age group (37.3%) compared to the non-adult age groups (2–11 years: 26.8%, 12–17 years: 26.9%). However, the share of patients aged 12–17 years and being dispensed TCI was higher (2.6%) in comparison with adult patients (1.9%) and those aged 2–11 years (1.4%). Dispensations of both TCI and TCS were more frequently observed in the age group of

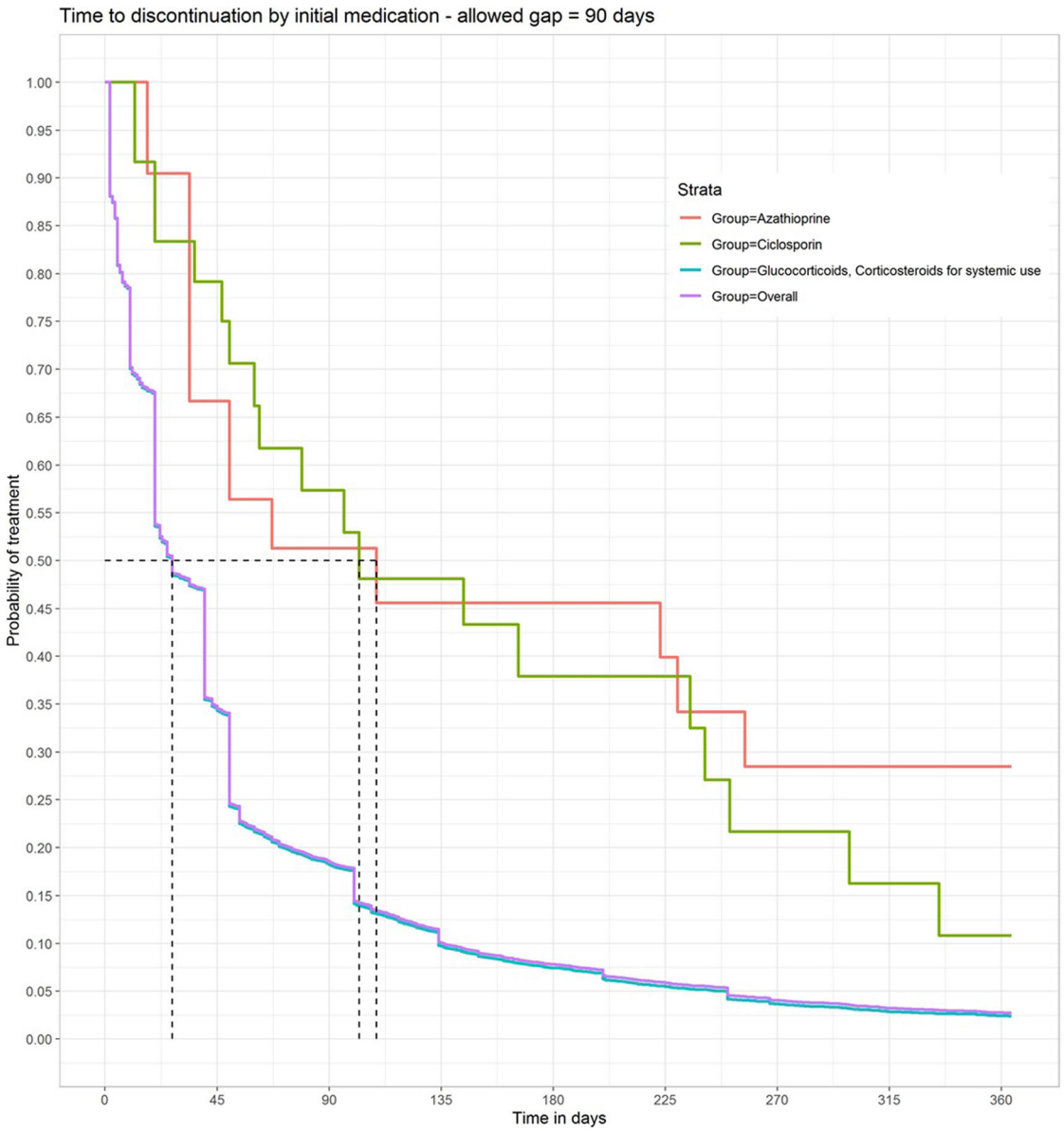

Fig. 3 Time until discontinuation of index systemic drug therapy, Kaplan–Meier curve

12–17 years compared to other age groups (2–-11 years: 3.5%, ≥ 18 years: 5.8%).

Within the adult age group, mean dispensed DDD of TCS were notably higher (109.4 mean DDD, SD 167.2) compared to the younger age groups (2–11 years: 40.7 mean DDD, SD 55.5; 12–17 years: 59.3 mean DDD, SD 68.3). In contrast, mean DDD of TCI were higher within non-adult patients (2–11 years: 25.9 mean DDD, SD 32.3, 12–17 years: 29.3 mean DDD, SD 43.1) compared to adult patients (22.9 mean DDD, SD 24.0).

HCRU and associated costs

HCRU and associated costs are presented in Tables 5 and 6.

Mean annual costs per patient for drug treatment were € 1237. Ninety-nine percent of the patients were observed with at least one

Table 4 Use of concomitant TCS and/or TCI during the 1-year observation period, stratified by age

	2–11 years (n = 2243)				12–17 years (n = 417)				≥ 18 years (n = 7315)				All (n = 9975)			
	n	%	Mean DDD	SD	n	%	Mean DDD	SD	n	%	Mean DDD	SD	n	%	Mean DDD	SD
Concomitant topical therapy																
Neither TCI nor TCS	1532	68.3			266	63.8			4024	55.0			5822	58.4		
TCS only	602	26.8	40.7	55.5	112	26.9	59.3	68.3	2732	37.3	109.4	167.2	3446	34.5	95.8	153.5
TCI only	31	1.4	25.9	32.3	11	2.6	29.3	43.1	137	1.9	22.9	24.0	179	1.8	23.8	26.9
TCI and TCS																
TCI	78	3.5	37.8	59.7	28	6.7	42.5	51.4	422	5.8	33.7	46.4	528	5.3	34.7	48.8
TCS	78	3.5	96.6	144.1	28	6.7	246.1	338.3	422	5.8	156.3	276.0	528	5.3	152.3	265.9

DDD defined daily dose, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroids, *SD* standard deviation

outpatient physician visit with on average 26.4 contacts per patient in the observation period. Outpatient services were associated with mean annual costs per patient of € 943. 2.3% of the patients had at least one documented outpatient visit for phototherapy associated with mean annual costs of € 101.

In the study cohort, 25.4% of the patients were observed with at least one hospitalization. Patients had on average 1.7 admissions (SD 1.6) with a mean duration of 13.0 days (SD 21.7). Associated mean annual costs per patient amounted to € 5836. At least one hospitalization due to AD was observed in 0.9% of the patients (mean number of admissions: 1.2 [SD 0.6], mean duration: 13.7 days [SD 15.3]). Associated mean annual costs per patient amounted to € 3455.

During the observation period, 43.2% of the adult patients in the study cohort were observed with having at least one documented sick leave due to any cause. Adults had on average 2.8 sick leaves (SD 2.2) with a mean duration of 33.5 days (SD 49.1). Sick leave due to AD in particular was observed within 3.3% of the patients. Those had on average 1.2 sick leaves due to AD with an average duration of 24.0 days (SD 48.7).

Claims for sickness benefits were observed in 5.6% (n = 341) of the adult patients. Associated mean annual costs per patient amounted to € 5026. Sickness benefits due to AD were observed in 0.4% (n = 22) of the adult patients (mean annual costs per adult patient: € 6235).

Summed up, all-cause direct and indirect costs were € 8016 and € 5026 per (adult) patient per year among patients with AD and SDTI, respectively. The direct and indirect annual costs per (adult) patient due to AD amounted to € 3677 and € 6235, respectively.

DISCUSSION

Summary of findings

The aim of this study was to describe current treatment patterns, HCRU and costs associated with managing patients with AD and SDTI in Germany. Based on data of a German health insurance database, 9975 (0.2%) patients with AD and SDTI were identified within the year 2017. Most of the patients with AD and SDTI (> 99.0%) used SCS as systemic medication; whereas use of SIS (azathioprine, cyclosporine, and methotrexate) and dupilumab was rare (each < 1%). Treatment duration for SCS, cyclosporine and azathioprine was 27 days, 102 days, and 109 days, respectively. Analysis of HCRU showed that 25.4% of the patients with AD and SDTI had at least one hospitalization whereas 0.9% had at least one admission due to AD. 43.2% had at least one sick leave and 3.3% had at least one sick leave due to AD. Among

Table 5 Healthcare resource utilization during the 1-year observation period, stratified by age

	2–11 years (n = 2243)						12–17 years (n = 417)						≥ 18 years (n = 7315)						All (n = 9975)					
	n	%	Mean	SD	Min	Max	n	%	Mean	SD	Min	Max	n	%	Mean	SD	Min	Max	n	%	Mean	SD	Min	Max
Outpatient services																								
No. of contacts	2242	100.0	14.1	9.1	1.0	116.0	417	100.0	17.1	13.4	1.0	98.0	7306	99.9	30.8	23.9	1.0	392.0	9965	99.9	26.4	22.3	1.0	392.0
Phototherapy*	0	0.0					< 5	–					226	3.1					230	2.3				
Hospitalizations																								
No. of admissions	319	14.2	1.4	1.0	1.0	14.0	73	17.5	1.7	1.5	1.0	9.0	2138	29.2	1.8	1.6	1.0	22.0	2530	25.4	1.7	1.5	1.0	22.0
No. of days	319	14.2	6.5	16.5	1.0	212.0	73	17.5	14.1	25.4	1.0	137.0	2138	29.2	13.8	21.7	1.0	303.0	2530	25.4	13.0	21.7	1.0	303.0
No. of admissions due to AD	12	0.5	1.4	0.9	1.0	4.0	5	1.2	1.8	0.8	1.0	3.0	77	1.1	1.2	0.5	1.0	4.0	94	0.9	1.2	0.6	1.0	4.0
No. of days due to AD	12	0.5	9.3	7.6	1.0	27.0	5	1.2	16.4	14.4	3.0	40.0	77	1.1	14.2	16.2	3.0	103.0	94	0.9	13.7	15.3	1.0	103.0
Sick leave (adults, n = 6127)																								
No. of sick leave													2648	43.2	2.8	2.2	1.0	48.0						
No. of days													2648	43.2	33.5	49.1	1.0	365.0						
No. of sick leave due to AD													200	3.3	1.2	0.5	1.0	5.0						
No. of days due to AD													200	3.3	24.0	48.7	1.0	359.0						

Numbers which are too low or might allow indirect calculability of too low case numbers cannot be displayed due to data protection reasons

AD atopic dermatitis, *SD* standard deviation

*Includes only outpatient phototherapy

Table 6 Healthcare resource utilization and associated costs in the 1-year observation period, stratified by age

	2–11 years (n = 2243)				12–17 years (n = 417)				≥ 18 years (n = 7315)				All (n = 9975)			
	n	%	Mean cost [€]	Sum [€]	n	%	Mean cost [€]	Sum [€]	n	%	Mean cost [€]	Sum [€]	n	%	Mean cost [€]	Sum [€]
Outpatient services																
Any contact	2242	100.0	507	1,136,386	417	100.0	610	254,199	7306	99.9	1096	8,005,964	9965	99.9	943	9,396,549
Phototherapy*	0	0.0	–	–	< 5	–	–	–	226	3.1	102	23,090	230	2.3	101	23,300
Hospitalizations																
Any admission	319	14.2	2291	730,958	73	17.5	5.082	370,993	2138	29.2	6391	13,664,133	2530	25.4	5836	14,766,085
Admission due to AD	12	0.5	3681	44,176	5	1.2	4.796	23,979	77	1.1	3333	256,611	94	0.9	3455	324,767
Medication																
Any drug therapy	2243	100.0	372	834,169	417	100.0	857	357,428	7315	100.0	1524	11,147,820	9975	100.0	1237	12,339,417
AD-related systemic drugs	2243	100.0	32	72,662	416	99.8	36	14,840	7302	99.8	68	497,104	9961	99.9	59	584,606
Other AD-related drugs (excl. systemic drugs)	1454	64.8	38	55,917	221	53.0	65	14,282	4026	55.0	71	286,048	5701	57.2	62	356,247
Concomitant use of TCI and TCS													4153	41.6	46	191,298
Sickness benefits																
Any sickness benefit	0	0.0	–	–	< 5	–	–	–	341	5.6	5026	1,713,841				
Due to AD	0	0.0	–	–	0	0.0	–	–	22	0.4	6235	137,167				

Numbers which are too low or might allow indirect calculability of too low case numbers cannot be displayed due to data protection reasons

AD atopic dermatitis, *SD* standard deviation, *TCI* topical calcineurin inhibitor, *TCS* topical corticosteroids

*Includes only outpatient phototherapy

adult patients with AD and SDTI, 5.6% received sickness benefits (all-cause) and 0.4% received sickness benefits due to AD. All-cause direct and indirect costs were € 8016 and € 5026 per (adult) patient per year among patients with AD and SDTI, respectively. Direct and indirect costs due to AD amounted to € 3677 and € 6235 per (adult) patient per year, respectively, in the population considered.

Discussion of findings

The focus of the present study was on patients with AD and SDTI, i.e., patients with a first documented health claim of systemic medication after a 1-year baseline period without a respective claim. Characteristics of patients with AD and SDTI showed a higher percentage of females (57.8%) and a majority of patients being 2–11 years old (22.5%). Consistent with other research [29], more male than female individuals were observed among young patients (< 18 years); whereas among adult patients, a female predominance was observed. Besides back pain and acute respiratory infections, in line with existing research literature [4, 30, 31], bronchial asthma was revealed to be one of the three most common comorbidities in the considered patient population. This seems expectable in light of epidemiologic and pathophysiologic parallels reported in the literature [32].

Within the present analysis, the majority of patients with AD and SDTI received SCS. Considering that evidence on the efficacy of SCS is sparse and guidelines discourage their use [12, 33], these results are remarkable. Since previous secondary [34–38] or registry data analyses [4, 39, 40] differ in terms of the patient population results can only be compared to a limited extent.

Consistent with this study, a current study from the US analyzing treatment patterns based on claims data, found SCS to be the most frequent systemic therapy initiated among patients with AD [41]. However, this work found a much higher proportion of patients initiating systemic drug therapy with SCS compared with the US study mentioned above (99.2% vs. 73.4%) [41]. Differences within study methodology (e.g., selection criteria, study period), as well as national differing prescribing practices, may serve as an explanation. For example, a recent study reported differences between North America and Europe concerning the choice of systemic therapy in pediatric patients with AD among dermatologists [42]. Diversity concerning prescribing practices in adult patients with AD was reported as well [43].

According to the guideline recommendations and a consensus paper of the International Eczema Council, SCS should mostly be prescribed due to an acute flare [11, 12, 33]. This suggests that the SCS subgroup comprised patients who were only treated systemically due to an acute flare but may not have been eligible for other systemic drug therapy options. However, since information on disease severity and prescription reason were not available in the analyzed database, the study results should be interpreted with caution in this regard.

In the present study, the probability of being under SCS-treatment after 27 days was still 50%. The actual reasons for the discontinuation of treatment were beyond the scope of this study and the abilities of the analyzed database. German guidelines recommend SCS treatment only over “a few weeks” while European guidelines even suggest a period of “up to 1 week” for the treatment of acute flares of AD [11, 12]. Considering the observed treatment duration within this study, the use of SCS in most cases was no longer in line with European guideline recommendations.

The study findings showed that SCS were also dispensed commonly in non-adult patients with AD and SDTI despite their known side effects (e.g., Cushing, osteoporosis, diabetes) [44]. Due to an unfavorable risk–benefit profile, guideline recommendations refer to a restricted usage of SCS to adult patients; whereas usage in non-adults should be handled cautiously [11, 12]. Although SCS are considered effective, risk of relapse is high [11]. Nevertheless, SCS were used in a large proportion of patients with AD. The rapid achievement of clearing the AD as well as a lack of other viable treatment options serves as a possible explanation [33, 45].

In the current study, only a small proportion of patients with AD and SDTI received other available systemic drug therapy options apart from SCS, for example the licensed drugs cyclosporine or dupilumab or off-label products such as azathioprine or methotrexate. While cyclosporine acts rapidly for acute flares of AD, it may be contraindicated in some patients.

Cyclosporine is recommended for short- and medium-term use in adult patients with chronic, severe AD and may be considered in children and adolescents with refractory, severe disease course (off-label < 16 years) [11, 12]. According to the German guideline, the ratio of expected benefits to risks must be examined individually against the background of therapeutic alternatives when using cyclosporine in the indication of AD [11]. It can be assumed that cyclosporine is only used from a certain disease stage onwards, weighing the benefits against the risk for side effects. Thus, concerning the observed rare use of cyclosporine, disease status and contraindications represent potential factors.

Dupilumab was approved for adults in September 2017 and adolescents in August 2019 [46]. Since it was only newly available for adults on the German drug market during the time of this study (the observation period covered only 1 year after index in year 2017), just a few dupilumab cases (0.3%) could be observed. In addition, dupilumab is recommended for patients with moderate-severe AD whose disease cannot be adequately treated with topical medication alone [11].

In contrast to other study findings [30, 41], the share of patients who received any dispensations for concomitant drug therapy by means of TCS/TCI was relatively low (41.6%). A claims data-based analysis of patients with AD using advanced therapies reported 65.2% receiving TCS; while 5.7% and 4.0% received tacrolimus and pimecrolimus [41]. A Japanese study reported an even higher rate with 86.7% of the patients with moderate-severe AD receiving TCS and/or TCI [30]. Extemporaneous preparation are drugs individually prepared by a pharmacist because an appropriate drug is not readily available. As the latter were not identifiable in the analyzed database, this may serve as an explanation for the high percentage (58.4%) of patients without any concomitant drug therapy by means of TCS and/or TCI in the study findings shown. TCS phobia, i.e., negative feelings and beliefs related to TCS, has been reported in the literature among patients with AD and their caregivers [47], which may also have contributed to the reduced number of patients receiving TCS and/or TCI in this study. Furthermore, patients were identified based on their first observable dispensation of systemic drug therapy in this analysis. Since claims data do not include information on reasons for prescriptions, it cannot be completely ruled out, that included patients received systemic drug therapy due to a comorbid condition other than AD.

In line with other international studies, the present findings show that HCRU of patients with AD and SDTI within German healthcare setting was primarily driven by outpatient visits and pharmacy prescriptions [34, 37].

There are some studies that analyzed AD-associated costs [21, 37, 41, 48]. However, comparability of these studies with the present study is limited due to differing target populations, different methodological approaches of cost determination, and large differences in the organization of the respective underlying healthcare (e.g., Germany vs. USA). In line with a German study from 2005, direct costs from the SHI perspective were mainly driven by costs of inpatient services, prescription drugs and outpatient services [21]. Nevertheless, direct costs were remarkably higher in the present study. One explanation may be that costs for inpatient services and medication have increased since then due to general cost developments and the introduction of new treatments. Another German study from 2021 showed that AD was associated with considerable out-of-pocket costs for healthcare (e.g., emollients), which can contribute substantially to total AD-associated costs [24]. Considering that the use of OTC medication could not be assessed within the present study, reported costs (for non-pharmacological topical AD treatments) were likely underestimated.

Strengths and limitations

The key strength of the present study was the large, unselected, and nationwide sample. Thus, estimations of patient characteristics, treatment patterns, and HCRU are likely to be representative [25]. Since the study was based on routinely collected health claims data, non-response or recall bias can be mitigated [49].

Nevertheless, the following limitations have to be kept in mind when interpreting the results of the study at hand. First, the InGef database comprises data of different German SHI companies; mainly, so-called "Betriebskrankenkassen" and "Ersatzkassen". Thus, estimates may be biased due to varying socio-demographic information and information on morbidity between the different types of SHI. However, as previous analyses addressing the external validity of the InGef database point towards good overall accordance of the dataset and the German population [12], biased estimates are unlikely in this study.

Second, German health claims data do not allow to obtain information on clinical parameters such as disease severity, reasons for treatment discontinuation, or reasons for prescriptions, as discussed above. Therefore, it cannot be clearly stated from the analyzed database whether the corresponding medication was actually used due to the AD diagnosis. Moreover, no time frame (such as one quarter) was specified in which both an AD diagnosis and the dispensation of systemic drug therapy had to be documented. Consequently, it cannot be clearly stated if systemic drug therapies as SCS were prescribed for AD or for any other comorbid indication (e.g., allergic diseases such as bronchial asthma) [16].

Third, some pharmaceuticals such as herbal remedies and OTC drugs are usually not reimbursed by the SHI for patients aged $\geq$ 12 years; whereas prescription drugs are covered in Germany. Since many of the non-pharmacological topical AD treatments are available as OTC, they are mostly not represented in health claims data and could therefore not be covered in the present analysis.

Concerning the analyses of sickness benefits and sick leave, it should be noted that not all patients are entitled to sickness benefits or may get sick leave. This includes freelancers and self-employed, pupils, students, pensioners, and the unemployed. Thus, analyses of sickness benefits and sick leave will therefore always lead to an underestimation of the actual burden. Additionally, it should be noted, that indirect costs included only sickness benefits. In Germany, sickness benefits are paid by the SHI funds from the seventh week of illness to entitled insured persons (see above). Since other cost elements, such as productivity losses or reduced work performance, were not considered, indirect costs can be assumed to be underestimated.

HCRU was assessed during the 1-year period following the first dispensation of a systemic medication after 1 year without a corresponding dispensation. Since no further restrictions to moderate-severe cases were applied, it can be assumed that less severe cases were potentially overrepresented.

Finally, the current study focused on the determination of current systemic treatment patterns within the German health care setting. Taking into account the new introduction of dupilumab at the end of 2017, the study period was chosen after its approval (2017/2018) accordingly. Yet, the time period chosen may not be fully representative of the current healthcare situation with regard to systemic drug therapy as it is likely that some patients may not have had access to dupilumab immediately after its approval.

CONCLUSIONS

This study provides real-world evidence of the current treatment patterns of systemic drug use and medical care situation of patients with AD in Germany. Whereas other systemic drug therapy options were rarely used, the results of this study indicate a common use of SCS in patients with AD and SDTI (including non-adult patients) in Germany. The results suggest that the duration of treatment with SCS and their frequent use in non-adult patients exceed the recommendations of current guidelines in the majority of cases. They further suggest a

substantial direct and indirect cost burden of patients with AD and SDTI.

The results of this study should be interpreted cautiously in light of the described limitations. Further research based on current real-world data is needed to investigate the changing treatment situation with the availability of dupilumab and other new systemic drug therapies in Germany.

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Compliance with Ethics Guidelines. Since all patient-level data in the database are anonymized to comply with German data protections regulations and German federal law, approval of an Ethics Committee was not required. The research was conducted in accordance with the Declaration of Helsinki.

Data Availability. The data used in this study cannot be made available in the

manuscript, the supplemental files, or in a public repository due to German data protection laws (Bundesdatenschutzgesetz). To facilitate the replication of results, anonymized data used for this study are stored on a secure drive at the InGef GmbH. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and can be assessed upon request, after written approval (info@ingef.de), if required.

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