ORIGINAL ARTICLE

Care pathways in atopic dermatitis: a retrospective population-based cohort study

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Abstract

Background Atopic dermatitis (AD) is a complex disease with variations in severity and healthcare utilization. Examining patient pathways through analyses of longitudinal patient data provides an opportunity to describe real-world clinical patient care and evaluate healthcare access and treatment.

Objective To describe longitudinal care pathways including health care management, treatment patterns and disease progression (by proxy measures) in patients with AD.

Materials and methods This was a longitudinal observational study, which used linked data from national and regional healthcare registers in Sweden. Patients with AD were identified through diagnosis in primary or secondary care or by dispensed medications. Descriptive statistics for number of healthcare visits, type of dispensed drug class, rate of - and time to - referral to secondary care and treatment escalation were calculated.

Results A total of 341 866 patients with AD distributed as 197 959 paediatric (age $<$ 12), 36 133 adolescent (age $\geq$ 12- $<$ 18) and 107 774 adult (age $\geq$ 18) patients were included in this study. Healthcare visits to primary and secondary care and dispensation of AD-indicated treatments were more common during the year in which managed AD care was initiated. Topical corticosteroids (TCSs) and emollients were the most frequently used treatments across all age cohorts while systemic treatment was uncommon in all age cohorts. Among patients who initiated treatment with TCSs, 18.2% escalated to TCSs with higher potency following the start of managed AD care.

Conclusions We found that healthcare contacts and use of AD-indicated treatments were concentrated in the year during which managed AD care was initiated and decreased significantly thereafter. Since a significant proportion of patients with AD have flares and persistent AD, our results suggest that patients with AD may be monitored infrequently and are undertreated. There is a need to inform practitioners about adequate treatment options to provide individualized care, in particular for patients with persistent severe AD.

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Conflicts of interest

Amy Cha, Joseph C. Cappelleri, and Maureen P. Neary are employed by Pfizer Inc. and own Pfizer stock and/or stock options. William Romero is employed by Pfizer Ltd and owns Pfizer stock and/or stock options. Dan Henrohn and Anna De Geer are employed by Pfizer AB and own Pfizer stocks. Petra Neregård was an employee of Pfizer AB and owned Pfizer stocks at the time of this work and is, at the time of manuscript submission, an employee of UCB Pharma AB. Laura von Kobyletzki has been consultant or speaker for Pfizer, Sanofi-Genzyme, Leo Pharma and Eli Lilly. Dr. Thyssen is an advisor for AbbVie, Almirall, Arena Pharmaceuticals, OM Pharma, Aslan Pharmaceuticals, Union Therapeutics, Eli Lilly & Co, LEO Pharma, Pfizer, Regeneron, and

Sanofi-Genzyme, a speaker for AbbVie, Almirall, Eli Lilly & Co, LEO Pharma, Pfizer, Regeneron, and Sanofi-Genzyme, and received research grants from Pfizer, Regeneron, and Sanofi-Genzyme. Natalia Ballardini has received consultancy fees from Sanofi, Pfizer and Galenica. Kirk Geale is an employee and board member of Quantify Research and owns Quantify Research stock options. Gustaf Ortsäter is an employee of Quantify Research and owns Quantify Research stock options. Alexander Rieem Dun is an employee of Quantify Research. Ingrid Lindberg was an employee of Quantify Research during the development of this manuscript, and is, at the time of manuscript submission, an employee of UCB Pharma AB. Quantify Research AB provides consulting and other research services to pharmaceutical, medical device, and related organizations. Quantify Research AB received funding from Pfizer Inc. to conduct this study and for the development of this manuscript.

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Abbreviations

AD: Atopic Dermatitis

ATC: Anatomical Therapeutic Chemical

CDR: Cause of Death Registry

ICD-10: International Classification of Disease version 10

LISA: Longitudinal Integration Database for Health Insurance and Labour Market Studies

M2M: Mild-to-moderate

NPR: National Patient Registry

OTC: Over-the-Counter

PDR: Prescribed Drug Registry

RSVD: Skåne Primary Care Database

SD: Standard Deviation

TCIs: Topical Calcineurin Inhibitors

TCS: Topical Corticosteroid

VEGA: Västra Götaland Primary Care Database

Background

Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is characterized by pruritus and eczematous lesions.[1] In roughly 60% of cases, this disease manifests during the first year of life, but may start at any age.[2,3] This disease gradually resolves in the majority of paediatric and adolescent patients (age < 18 years at diagnosis) when they enter adulthood, but in some patients this condition persists and patients have flares of AD into adulthood.[4,5] Patients with AD have an increased risk of developing numerous burdensome comorbidities.[6–10] As such, different parts of the healthcare system and different specialized clinics might see patients suffering from AD.[11]

Disease management aims at improving signs and symptoms of AD and at achieving long-term control. Milder forms of AD are routinely managed in primary care.[12] However, AD is a chronic, relapsing–remitting condition that is often characterized by periods of disease exacerbation, sometimes lasting for years. Emollients and bath oils, together with education and identification of patient-specific allergens and irritants are part of the management of all AD patients. Topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) are first-line anti-inflammatory treatment options (TCIs from 2 years of age). Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application. Hence, the potency of TCSs should be increased with the severity of the disease. Phototherapy is also recommended for adolescents and adults with moderate to severe AD. Specialized care is periodically required for managing severe AD[13,14] and systemic immunosuppression is recommended using medications with a favourable safety profile.

AD is a complex disease with variations in severity and in associated healthcare utilization that may not yet be fully understood. Examining patient pathways through longitudinal patient data provides an opportunity to describe real-world clinical patient care and highlight issues related to healthcare access and treatment.[15] Further, understanding how care pathways are linked to disease severity will help decision makers to quantify the economic benefits of disease management. In recent years, several new treatment options in AD have gained regulatory approval and are expected to reach the market within the next several years.[16] It is important to understand disease duration, severity and patient pathways in terms of healthcare utilization, current management, and the use of existing treatment options, to provide AD patients with optimal care.

The objective of this study was to describe longitudinal care pathways including healthcare management, treatment patterns and disease progression (by proxy measures) for AD in Sweden.

Sweden maintains administrative data with complete population coverage that provides excellent conditions for describing longitudinal patient pathways, given its breadth and recordings of ICD-10-, procedure- and ATC codes. By using a population-

based database with access to data from different parts of the healthcare system, patient pathways and disease severity can be explored in a comprehensive manner.

Methods

Data sources and ethics

This study used retrospective administrative data from Sweden to address the study objectives. Data were extracted from the National Patient Registry (NPR), which contains medical information for all in- and outpatient specialist (secondary care) visits, including ICD-10 codes and dates; the Prescribed Drug Registry (PDR), which includes data for all pharmacy-dispensed medications (Anatomical Therapeutic Chemical [ATC]-codes) and pharmacy dispensation dates; and the Cause of Death Registry (CDR), which contains data on cause and date of death. These three databases are managed by the Swedish National Board of Health and Welfare and require mandatory reporting, thereby resulting in complete population coverage. Data were also extracted from regional primary care databases from the Västra Götaland and Skåne regions (VEGA and RSVD, respectively).

The regional primary care databases cover approximately 1/3 of the Swedish population. Data include diagnosis codes (International ICD-10) and corresponding dates for visits. Socioeconomic data including household income and migration information used to censor patients who emigrate from Sweden, were extracted from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA). Data from all databases were available from 1 July 2005 until 31 December 2018, which determined the study period. All data were linked at the patient level using personal identification numbers included in each registry.

Ethics approval for this study was obtained from the Ethical Review Board in Sweden (reference number 2019–03840).

Study population and study design

A cohort of patients with AD identified between 2007–2017 (inclusive) was included in this study. AD in patients 18 years of age and older was defined using a registered diagnosis of AD (ICD-10: L20+) in primary- (VEGA or RSVD) or secondary care (NPR). Using a validated case-finding AD algorithm,[17] patients under 18 years of age were identified as having AD if they met at least one of the following two inclusion criteria:

1 At least one diagnosis of AD (ICD-10 L20+) registered in NPR, VEGA or RSVD.
2 At least one dispensation of a TCI (ATC D11AH+) or at least two dispensations of a TCS (ATC D07+) within 12 months of each other and one of these dispensations should belong to the mild-to-potent group (corresponding to class I-III following the European classification system for the potency of TCSs, which was used in this study[18]) of TCSs as AD is usually never treated alone with a very potent TCS.

Patients meeting the 2nd inclusion criterion only and who have had healthcare visits related to diseases other than AD were excluded since TCSs are indicated for many diseases and alone are a poor proxy measurement for an AD-diagnosis.[19] Moreover, patients with dispensations of antipsoriatics, salicylates for dermatological use, combinations of salicylates and moderate/potent TCSs, potent TCSs in combination with antibiotics, and potent TCSs in combination with antifungals were also excluded.[17] Since no algorithm can be completely accurate for use in case-identification, a sensitivity analysis was performed in which AD in patients under 18 years of age was defined using only a registered diagnosis of AD (L20+) in VEGA, RSVD or NPR (i.e. only inclusion criteria 1).

The date of first AD-diagnosis during the study period was defined as the index date, that is start of follow-up. The study population was stratified into three cohorts based on age at index date, paediatric (age < 12 years), adolescents (age ≥ 12- < 18) and adult (≥18 years) patients. Inclusion started on 1 January 2007, which enabled at least 18 months of look-back for all individuals. The look-back period was implemented to ensure that the index date represented the initiation of AD care management given at least 18 months without clinically managed disease activity. The look-back period was also used to collect baseline characteristics including presence of comorbidities. Study enrolment ended on 31 December 2017 and the study period ended on 31 December 2018, allowing all included study subjects to have a minimum of 1 year's follow-up. Patients were censored at death or emigration. Moreover, paediatric patients were censored when they entered adolescence and adolescents were censored when they entered adulthood. The study design is provided in Fig. 1.

Disease progression as assessed by proxy measures

Patients' baseline severity was defined according to the type of AD-indicated treatment (from now on referred to 'AD-treatment') or number of healthcare visits with an AD-diagnosis that occurred in the 365 days prior to the index date and up through 30 days after index date. The criteria are outlined in Table 1. AD-treatment included topical therapies (emollients, TCSs and TCIs) and systemic therapies (azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, systemic corticosteroids prescribed by dermatologist, dupilumab[†] and phototherapy). Severity was defined at baseline and fixed throughout follow-up in all analyses except for the analysis of disease progression in which severity was updated on an annual basis. Disease progression was defined using proxy measures of

[†]No or very limited dupilumab use was anticipated given that our study enrolment period closed before dupilumab was reimbursed for patients in Sweden. Dupilumab was only reimbursed during the last 7 months of this study (follow-up period only).

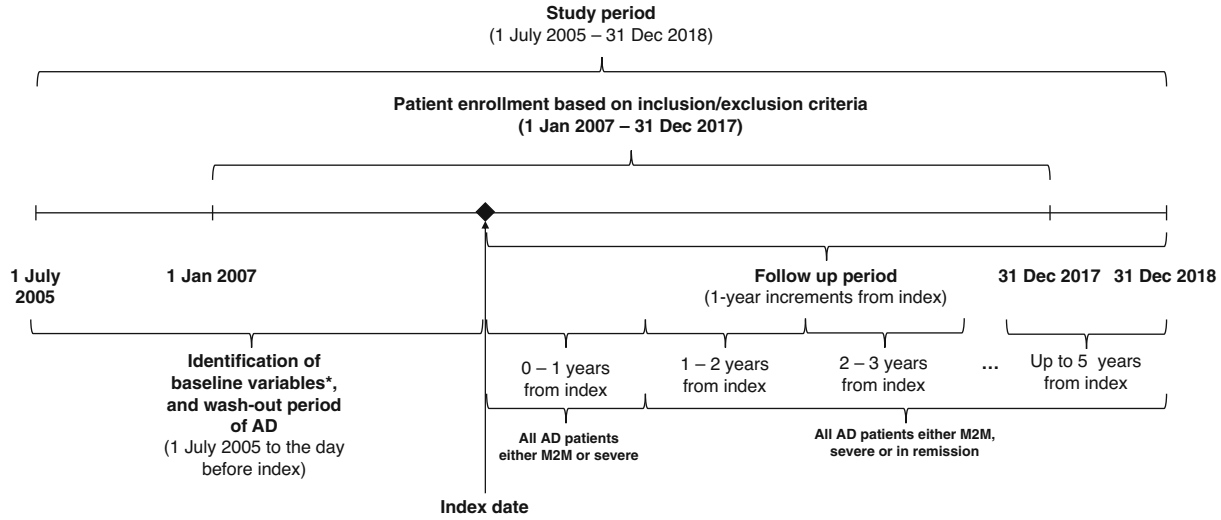

Figure 1 Schematic of study design: *Exceptions: Baseline disease severity was defined at index to – and including – 1 year after index, socioeconomic variables (income, education and employment) were defined in the calendar year prior to index, age and gender at index date, and healthcare resource use during 1 year prior to index date.

Table 1 Algorithm to define severity of AD

	Paediatric and adolescent patients	Adult patients
Severe AD	• Dispensation of potent† or very potent TCS • Dispensation of dupilumab • Dispensation of systemic immunosuppressant treatment • Dispensation of systemic corticosteroids from dermatologist • Two or more secondary care visits with an AD-diagnosis (principal or secondary diagnosis) • Phototherapy in secondary care	• Dispensation of very potent TCS • Dispensation of dupilumab • Dispensation of systemic immunosuppressant treatment • Dispensation of systemic corticosteroids from dermatologist • Phototherapy in secondary care
Mild-to-moderate AD	• Dispensation of TCI • Dispensation of mild or moderate TCS • Dispensation of emollients • Primary care visit with an AD-diagnosis (principal or secondary diagnosis) • Phototherapy in primary care • No more than one secondary care visit with an AD-diagnosis as principal diagnosis • One or more secondary care visit with an AD-diagnosis as secondary diagnosis	• Dispensation of TCI • Dispensation of mild, moderate or potent TCS • Dispensation of emollients • Primary or secondary care visit with an AD-diagnosis (principal or secondary diagnosis) • Phototherapy in primary care
Non-active AD‡	• None of the above	• None of the above

†Adolescent patients were required to have two dispensations to be classified as severe AD.
‡Non-AD was only used when evaluating disease progression. Due to the requirements of the inclusion criteria, a patient could only be classified as non-active in the year following the inclusion year.

healthcare visits and treatment patterns, with data evaluated on an aggregate level.

Statistical analyses

Descriptive statistics for patient characteristics were computed for all patients: Means and standard deviations (SD) were reported for continuous variables while percentages were calculated for categorical variables. Means and medians were calculated for AD-related (principal diagnosis L20) primary- and secondary care visits in each follow-up year from index date, stratified by age cohort. The proportion of patients who had at least one dispensation of an AD-treatments was calculated on a

quarterly basis. In addition, treatment experience (any dispensed AD-treatment during the 365 days prior to index date), time to and type of first dispensed treatment after index date, treatment escalation (defined as switch to a more potent TCS or use of systemic treatment following topical treatment) was evaluated in the first year following index date. Also, the number of patients referred from primary care and time to appointment with secondary care was calculated. This study was descriptive in its nature and no statistical testing was conducted. All data handling and computation of descriptive statistics were performed in Stata 16.

Results

Patient characteristics

A total of 341 866 patients with AD were included in this study. Of these, 197 959 were paediatric patients, 36 133 were adolescents and 107 774 were adults. Descriptive statistics for patient characteristics are provided in Table 2. In the paediatric cohort, 46.7% of patients were female and 84.6% were classified to have M2M AD and 15.4% to have severe AD. In the adolescent cohort, 59.4% of patients were female and 85.0% were classified as having M2M AD and 15.0% as having severe AD. In the adult

Table 2 Summary of Patient Characteristics

	Paediatric patients ***N*** **= 197 959**	**Adolescent patients** ***N*** **= 36 133**	**Adult patients** ***N*** **= 107 774**
Age at index date, years (SD)	3.31 (3.20)	15.20 (1.73)	42.86 ()
Household income†, 1000€ (SD)	44.09 (46.57)	51.25 (38.68)	40.92 (70.67)
Healthcare resource use‡			
Outpatient visits, *n* (SD)	1.37 (2.50)	1.08 (2.72)	1.94 (3.97)
Inpatient care, days (SD)	0.68 (5.25)	0.35 (5.11)	0.86 (6.24)
Medications, number of unique dispensations (SD)	5.47 (50.70)	5.59 (42.34)	16.30 (50.14)
AD-identification, *n* (%)			
Diagnosis in secondary care	65 594 (33.1)	5746 (15.9)	63 099 (58.5)
Diagnosis in primary care	25 199 (12.7)	3902 (10.8)	44 675 (41.5)
Dispensation of TCS	112 925 (57.0)	25 821 (71.5)	N/a
Dispensation of TCI	2272 (1.1)	1557 (4.3)	N/a
AD-severity§, *n* (%)			
Mild-to-moderate AD	167 418 (84.6)	30 730 (85.0)	92 413 (85.7)
Severe AD	30 541 (15.4)	5403 (15.0)	15 361 (14.3)
Female, *n* (%)	92 527 (46.7)	21 447 (59.4)	69 627 (64.6)
Employed, *n* (%)†	N/a	N/a	67 304 (62.4)
Highest education, *n* (%)†			
Below high school	N/a	N/a	67 451 (62.6)
High school	N/a	N/a	16 019 (14.9)
Above high school	N/a	N/a	24 304 (22.6)
Comorbidity profile¶, *n* (%)			
Neurological & psychiatric disorders	4622 (2.3)	4111 (11.4)	10 183 (9.4)
Hypersensitivity & allergic disorders	42 619 (21.5)	5816 (16.1)	16 554 (15.4)
Infections	65 651 (33.2)	4772 (13.2)	3602 (3.3)
Immunological and inflammatory disorders	1563 (0.8)	1046 (2.9)	4102 (3.8)
Skeletal disorders	5573 (2.8)	4896 (13.5)	10 840 (10.1)
Type 1 diabetes	386 (0.2)	230 (0.6)	1144 (1.1)
Type 2 diabetes	10 (0.0)	15 (0.0)	2605 (2.4)
Endocrine and metabolic disorders (excluding type 1 and type 2 diabetes)	3623 (1.8)	992 (2.7)	6330 (5.9)
Cardiovascular disease	304 (0.2)	79 (0.2)	11 599 (10.8)
Malignancies	287 (0.1)	104 (0.3)	5381 (5.0)
Ocular disorders	536 (0.3)	314 (0.9)	7767 (7.2)

All variables were reported at index date except when:
†Measured during the calendar year prior to index date.
‡Measured during the 365 days prior to index date.
§Measured from the 365 days prior to index date through 30 days after index date.
¶Measured from 01 July 2005 to – and including – index date.
Variables not relevant for the cohort in question were reported as N/a.
Abbreviations: SD = Standard deviation.

cohort, 64.6% of patients were female and 85.7% were classified as having M2M AD and 14.3% as having severe AD. The prevalence of comorbid conditions, except for hypersensitivity and allergic disorders and infections, was low during the look-back period.

Healthcare resource use in patients with AD

Healthcare contacts within both primary and secondary care with an AD-diagnosis as principal diagnosis were more frequent during the first year following index date compared to subsequent years in all three age cohorts. Figure 2 (Data is given in Table S1) shows the average number of secondary and primary care visits per year during follow-up. HCRU by severity at baseline is shown in Table S2.

Paediatric and adolescent patients On average, a paediatric patient visited secondary care 0.49 times and primary care 0.45 times in the first year following index date. In the second year of follow-up, the average number of visits to secondary and primary care were 0.12 and 0.07, respectively, and only 8% of patients had a visit to secondary care with an AD-diagnosis as primary diagnosis in the second year (data not shown). In the third and fifth year of follow-up, only 6.9% and 4.7% of paediatric patients had any AD-related contact with primary or secondary care (data not shown). In adolescent AD patients, the average number of visits to secondary and primary care in the first year following index date were 0.19 and 0.37, respectively.

Adult patients In the adult cohort, patients had on average 0.79 secondary care visits and 0.59 primary care visits in the first year following index date. In the second year following index date, the corresponding numbers were 0.11 secondary care visits and 0.06 primary care visits.

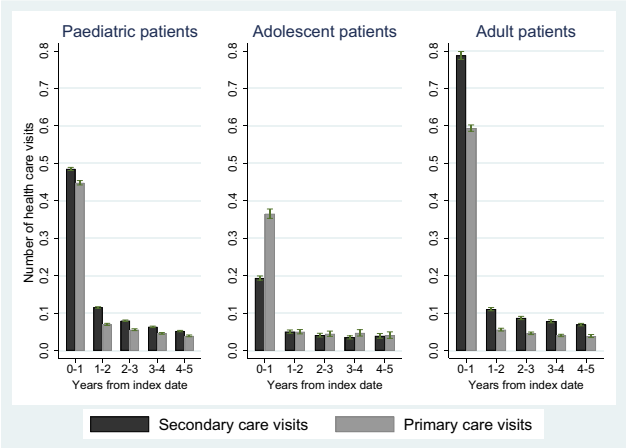

Figure 2 Mean number of annual AD-related healthcare visits after index by patient: AD-related healthcare resource use (HCRU) from index date and the 5 years thereafter. The error bars represent the 95% confidence intervals.

Treatment patterns in patients with AD

Similar to the results for healthcare contacts, dispensations of AD-treatment were also highest during the first year after index and then declined. TCSs and emollients were the two most common types of AD-treatments used across all age cohorts.

Paediatric and adolescent patients Figure 3 shows the percentage of patients with a dispensed prescription by treatment type over time (quarterly periods) in paediatric and adolescent patients. The use of topical therapies in paediatric and adolescent patients with severe AD (see Fig. S1) was slightly more sustained compared to M2M patients but declined over time in a similar pattern as observed in Fig. 3. Rates of use of systemic therapy were low in both paediatric and adolescent patients with severe AD (see Fig. S2).

In paediatric AD patients, 79.4% and 50.2% were dispensed at least one prescription of a TCS and emollients in the first year following index date, respectively (See Table S3). Emollients followed by mild TCSs continued to be the most frequently dispensed AD-treatment, but the usage decreased over time. In adolescent patients with AD, 86.9% had received a dispensation of a TCS in the first year following index. Potent TCSs were the most common type of treatment throughout the follow-up period while very potent TCSs (<2%) and TCIs (<6%) were seldom used. In paediatric patients with M2M AD, 20.9% were dispensed a TCS of higher potency after their initial dispensation, and the corresponding data in the severe AD paediatric cohort was 12.5%. Of those patients with an initial diagnosis in primary care, only 5.7% were referred to secondary care. The use of TCIs and systemic treatments was uncommon in paediatric patients with severe AD. In the first year following start of treatment with conventional systemic treatment 20.0% of the paediatric AD group were dispensed a TCS, and in the adolescent cohort, the corresponding data were 13.3% in the M2M group and 28.2% in the severe AD group. Moreover, in the first year following start of treatment with conventional systemic therapy 9.3% and 15.5% of the severe paediatric and adolescent AD patients, respectively, were dispensed a potent or very potent TCS as add-on. Detailed data for care patterns in the first year following index date are shown in Table 3.

Adult patients TCSs and emollients were the most frequently used treatments in adult patients (see Fig. 4). In the first year following diagnosis, potent TCSs were the most frequently used type of TCS by adult patients (65.2%). The use of systemic therapies in the first year following index date was low (1.9%, 2.5% and 2.4% using conventional systemic therapy, systemic corticosteroids prescribed by a dermatologist or phototherapy,

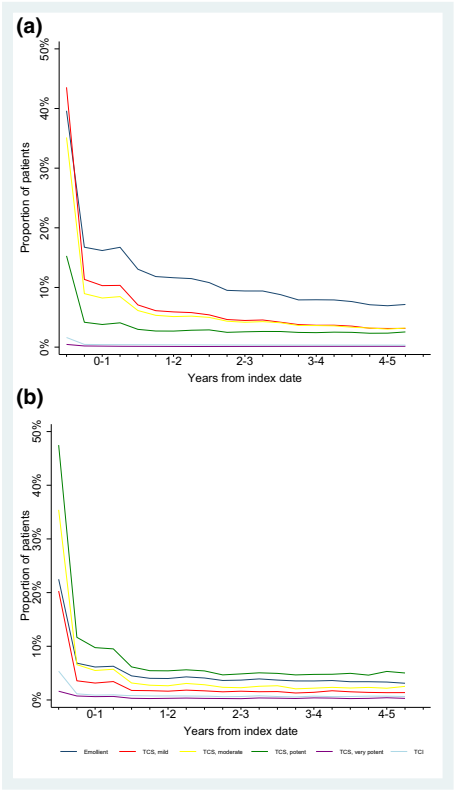

Figure 3 Proportion of patients with at least one prescription of topical therapies: in A) paediatric patients (top panel) and B) adolescent patients (bottom panel) following index date.

respectively). Dupilumab was not prescribed to any patient in the first year following index date. Use of systemic therapy in patients with severe AD was also low albeit 10.6% of adult patients with severe AD were dispensed systemic corticosteroids prescribed by a dermatologist in the first quarter following index date. This use then declined in these patients and other systemic therapies were used by less than 2% of the patient population with severe AD at baseline (see Fig. S3). Of those 8047 adult patients with severe AD whose first dispensation was a mild (907 patients), moderate (1564 patients) or potent (5576 patients) TCS (and could hence escalate TCS potency), 3693 (45.9%) had a subsequent dispensation of TCS with a higher potency. In adult patients with M2M AD, only 13.1% had a subsequent dispensation with a higher potency than their first dispensed TCS. Of those patients with severe AD whose first dispensed treatment was a conventional systemic therapy, 49.4% needed addition of a TCS or a TCI to their systemic therapy. In 36.6% of the patients, the added topical treatment was either a potent or a very potent TCS. In the group for which the first dispensed treatment was a conventional systemic therapy, 4.7% of the patients needed an oral steroid as add-on during the first year following start of conventional systemic therapy. Referral to secondary care was uncommon in both severity groups and time to referral was slightly more than 3 months (Table 3).

Disease progression as assessed by proxy measures in AD patients

Disease progression over time in the different age cohorts is shown in Fig. 5. Most patients did not have any AD-related healthcare visits nor AD-treatment dispensations in the second year following index and were hence classified as having non-active AD. Of those patients whose disease was classified as non-active in the second year, 85.3%, 51.3% and 90.0% were classified as M2M in the previous year in the paediatric, adolescent and adult cohorts, respectively. Worsening of the disease occurred in approximately 6% of paediatric and adolescent patients between year 1 and 2. In the adult cohort, only 3.7% of the cohort was classified as having severe AD after being classified as M2M in the first year. The proportion of patients having active AD (M2M or severe) continued to decrease after year 2 in all age cohorts, however, at 5 years after index date, 26.4%, 23.1% and 36.1% in the paediatric, adolescent and adult cohort, respectively, were classified as having either M2M or severe AD.

Sensitivity analysis

A sensitivity analysis with an inclusion criterion of a diagnosis code of AD in either primary- or secondary care only that was conducted in the paediatric and adolescent population yielded similar results as in the base case analysis. The results from the sensitivity analysis are shown in Fig. S4 and Table S4. Use of topical treatments was shown to be slightly lower in the sensitivity analysis compared to the base case but followed a similar decreasing trend over time. The frequency of AD-related primary- and secondary healthcare contacts was observed to be greater in the sensitivity analysis compared to the base case analysis, probably due to the design of the inclusion criteria, which required all patients to have a healthcare contact to be included in the sensitivity analysis.

Discussion

Principal findings

This large register-based cohort study of care patterns in patients with AD showed that the frequency of HCRU was associated with time since diagnosis and that the type of HCRU was dependent on the age of the patient. Although emollients and TCSs are recommended in guidelines as basic treatments for AD and were the most frequently dispensed AD-related treatments, less than half of the patients with AD received a dispensation for emollients. The underlying reasons for this are probably a mix of factors including, among others, satisfactory symptom-response from using other agents (TCSs), perceived lack of effect by the patient, and lack of awareness by some prescribing physicians of

Table 3 Care pathways in the first year following index date, by age cohort and severity at baseline

	Paediatric patients		Adolescent patients		Adult patients	
	Mild-to-moderate AD	Severe AD	Mild-to-moderate AD	Severe AD	Mild-to-moderate AD	Severe AD
Treatment experience, *n* (%)	26 130 (15.6)	6028 (19.7)	2674 (8.7)	485 (9.0)	39 705 (43.0)	12 464 (81.1)
First dispensed treatment after index date†, *n* (%)						
Topical corticosteroids	124 746 (74.5)	29 247 (95.8)	25 774 (83.9)	5267 (97.5)	60 680 (65.7)	12 162 (79.2)
Mild TCS	74 866 (44.7)	7005 (22.9)	6203 (20.2)	450 (8.3)	8315 (9.0)	907 (5.9)
Moderate TCS	57 230 (34.2)	4305 (14.1)	11 342 (36.9)	596 (11.0)	15 510 (16.8)	1564 (10.2)
Potent TCS	1148 (0.7)	22 942 (75.1)	10 621 (34.6)	4547 (84.2)	43 397 (47.0)	5576 (36.3)
Very potent TCS	68 (0.0)	509 (1.7)	29 (0.1)	235 (4.3%)	732 (0.8)	6773 (44.1)
Emollient	56 459 (33.7)	8920 (29.2)	5743 (18.7)	911 (16.9)	17 241 (18.7)	3418 (22.3)
TCI	2382 (1.4)	225 (0.7)	1553 (5.1)	99 (1.8)	8389 (9.1)	1081 (7.0)
Conventional systemic therapy	24 (0.0)	56 (0.2)	20 (0.1)	37 (0.7)	66 (0.1)	609 (4.0)
Systemic corticosteroids	n/a	n/a	8 (0.0)	32 (0.6)	105 (0.1)	1314 (8.6)
Phototherapy	n/a	n/a	n/a	n/a	37 (0.0)	222 (1.4)
Treatment escalation, *n* (%)						
Increase in TCS potency‡	27 905 (20.9)	4287 (12.5)	5078 (18.0)	627 (11.2)	8804 (13.1)	3693 (45.9)
Escalation to systemic therapy	137 (0.1)	161 (0.5)	148 (0.5)	113 (2.1)	1160 (1.6)	1592 (11.1)
Add-on of topical therapy (TCS or TCI) following systemic therapy§	5 (20.0)	16 (21.3)	4 (13.3)	21 (29.6)	76 (36.5)	1049 (49.4)
Add-on of TCS following conventional systemic therapy§	5 (20.0)	15 (20.0)	4 (13.3)	20 (28.2)	69 (33.2)	968 (45.6)
Add-on of potent or very potent TCS following systemic therapy§	n/a	7 (9.3)	n/a	11 (15.5)	55 (26.4)	778 (36.6)
Add-on of oral steroid following conventional systemic therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	39 (4.7)
Patients with referral to secondary care¶, *n* (%)	1303 (5.8)	218 (8.3)	133 (3.5)	26 (5.3)	1429 (3.42)	162 (5.64)
Time to referral¶, days (SD)	111.42 (98.92)	84.94 (93.65)	138.41 (106.34)	94.73 (71.90)	117.31 (97.82)	113.38 (114.23)

All estimates refer to the first year following index.
†The same patient may have a dispensation of agents in several different treatment classes as first treatment and, therefore, could be included in several groups.
‡Only patients with a mild to potent TCS as the first dispensed treatment after index were eligible in the analysis of increase in TCS potency.
§Only patients with a systemic therapy as first dispensed treatment after index were eligible in the analysis of add-on of topical therapy and topical therapy only included TCS and TCI.
¶Only patients with a diagnosis from primary care were included.
Dupilumab was not included since no patient was dispensed dupilumab in the first year following index date.
Abbreviations: TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitor, SD = standard deviation.

potential benefits for use of prescribed emollients. Economic resources should not explain the low use in children since prescribed medications (including emollients) are fully subsidized in Sweden in this age group but may be a factor for adult patients (emollients are not fully subsidized for adult patients). In addition, emollients may also be purchased over-the-counter (OTC) and would hence not be captured by our database. In a significant proportion of patients with AD, in particular patients with severe AD, symptoms persisted and required continuous management. The rate of referral to secondary care was low, and few patients had escalation of treatment to more potent TCSs or to systemic treatments. Potent topical treatments were often added to systemic treatments in adults with severe AD, suggesting that these patients do not reach a satisfactorily treatment response with systemic treatments.

Strengths and limitations

To the best of our knowledge, this is one of the largest studies to date to investigate the care pathways of AD patients and the first of its kind in Sweden. A major strength of this study is the access to data from both primary- and secondary care, which enabled us to examine care pathways and disease progression in a comprehensive manner. Moreover, the near complete coverage and long follow-up period in the Swedish databases increase the robustness and the external validity of our results. This study provides insights into the care pathways across all severities, as this study unlike other studies[20–22], identified patients with AD from both primary and secondary care registries.

Despite its strengths, we acknowledge that this study has some limitations. It lacked clinical data on validated severity measures for AD (e.g. EASI or SCORAD), relying instead on a severity

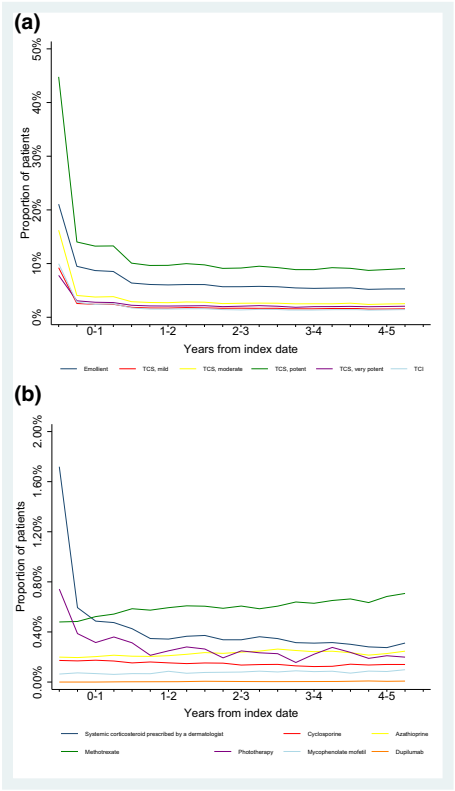

Figure 4 Proportion of adult patients with at least one prescription of topical therapies (top panel) and systemic therapies (bottom panel).

algorithm as a proxy for severity based on registered diagnoses and treatment use.

Furthermore, this study only included two regional primary care databases and therefore, for a part of the study population, healthcare contacts within primary care were not observable. This limitation is partly mitigated by the fact that the PDR covers pharmacy-dispensed medications originating from both primary and secondary care. By using a case-finding AD algorithm, patients and treatment patterns for patients from primary care regions, which were not included in this study could still be analysed. The results from the sensitivity analysis (patient identification using only a diagnosis code) yielded similar results as the base case, assuring that the results are robust to any misclassification that can occur when an algorithm is employed. Finally, OTC medications were not captured in the databases, underestimating the actual usage of treatments, in particular emollients and mild TCSs and, therefore, possibly excluding patients with mild AD.

Interpretation and comparison with other studies

Observed treatment rates in our study were in general lower compared to a study conducted in Danish patients (children and adults) with AD.[20] Also, a larger proportion of patients in the Danish study used TCSs with higher potency and dispensations of TCIs and use of systemic therapies was more frequent compared to that observed in our study. These differences are probably partly explained by the fact that the Danish study solely included patients based on referral to hospital-based dermatology clinics but also highlights the important role that dermatologists or other physicians with experience in treating AD play in the management of AD to provide adequate care and treatment.

The percentage of patients referred to secondary care was low in our study but is similar to results from a UK study on healthcare visits and treatment patterns in a primary care setting (23). The UK study found that the rate of referrals was associated with socioeconomic background, but this was not investigated in our study.[21]

Furthermore, as mentioned previously, lack of clinical data on severity measures prevented us from drawing firm conclusions on whether the sharp decline in use of AD-treatment, low rates of follow-up, referral and treatment escalation were indicative of symptom-resolution or if AD management can be improved. However, the high symptom burden reported by patients with AD suggests that the observed low healthcare use in this study is associated with suboptimal AD management rather than symptom-resolution.[23,24]

Suboptimal treatment may not only have a negative impact on patients' quality-of-life but may also cause unnecessary costs to the healthcare system. In a Danish cost of illness study, the number of primary care visits decreased after referral to the hospital setting indicating that adequate treatment reduces the patients' need for consultations.[25] Suboptimal treatment of AD may also be troublesome from a more holistic disease management perspective, where evidence shows that AD is a chronic systemic disease, with various AD-related comorbidities, which should also be monitored and managed appropriately.[26]

Conclusions

We found that the frequency of health care contacts and use of AD-treatments was concentrated in the year during which managed AD care began, and follow-up of patients was not common. Although most patients with AD were initially treated with topical treatments, usage declined substantially over time. Rates of referral and use of systemic treatments or higher potency TCSs were low for AD patients in Sweden. Given that previous evidence has shown that a significant proportion of patients with AD have flares and persistent AD, our results suggest that patients with AD are monitored too infrequently and are undertreated. There is a need to inform practitioners about adequate treatment options to provide individualized care, in particular for patients with persistent severe AD.

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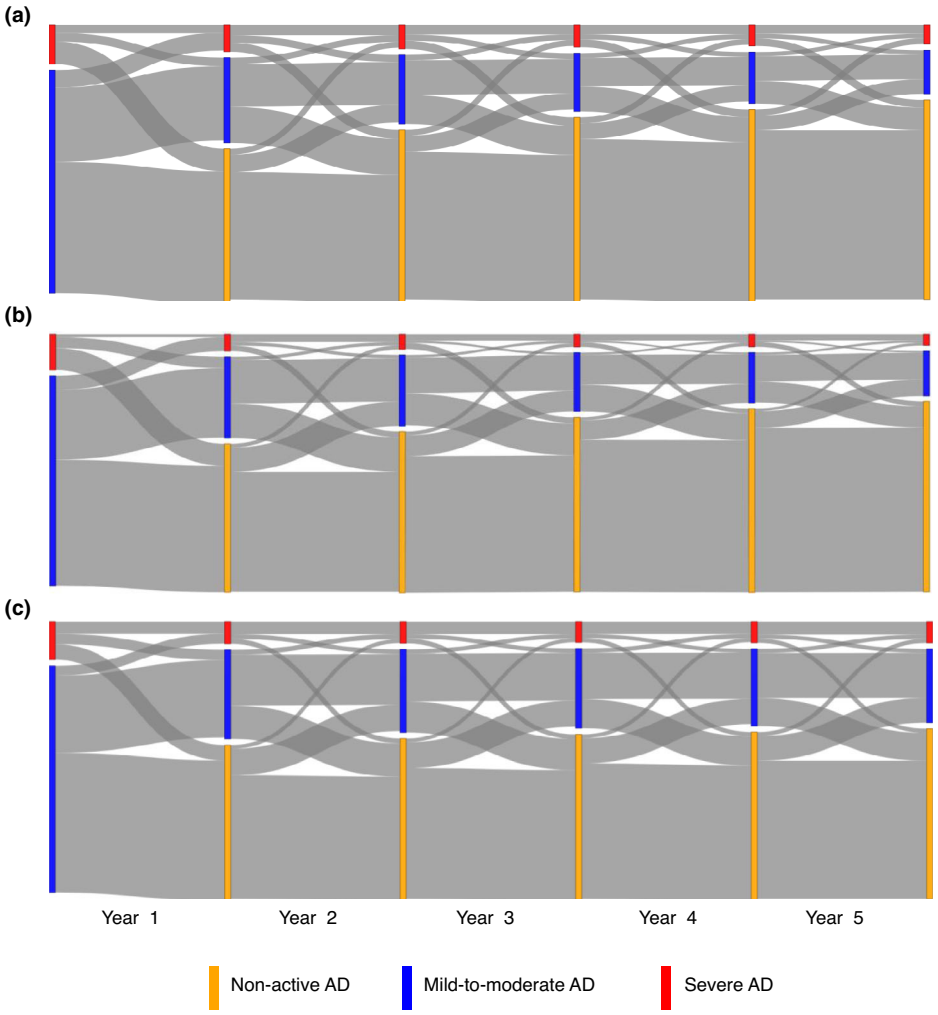

Figure 5 AD disease progression over time: This figure shows the proportion of patients by disease severity and transitions between severity groups over time after index date. Panel A shows paediatric patients, panel B shows adolescent patients and panel C shows adult patients.

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Author contributions

All authors participated in the conceptualization and design of this study. G Ortsäter, A Rieem Dun, K Geale and I Lindberg were involved in data curation, formal analysis, investigation, provision of resources, software programming and creation of visualizations. D Henrohn, MP Neary, P Neregård, A De Geer, A Cha and JC Cappelleri were involved in supervision and validation of the work. MP Neary acquired financial support for the study leading to this publication. L von Kobyletzki, N Ballardini and JP Thyssen provided clinical expertise. G Ortsäter, A Rieem Dun, K Geale and I Lindberg drafted the manuscript. All authors reviewed and approved the final manuscript. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have provided final approval of the version to be published.

Data availability statement

Data used in this study is protected under Swedish and European law and may only be accessed following relevant ethical

approvals, data protection assessments, and compliance with GDPR and other legal frameworks.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Healthcare resource use in AD patients, by age-cohort.

Table S2. Healthcare resource use in AD patients, by age-cohort and severity.

Table S3. Proportion of patients with at least one dispensation of AD-related therapy, by age-cohort and severity.

Table S4. Healthcare resource use in paediatric and adolescent patients, sensitivity analysis.

Figure S1. Proportion of patients with at least one prescription of topical therapy over time in a) paediatric patients and b) adolescent patients with severe AD.

Figure S2. Proportion of patients with at least one prescription of systemic therapy over time in a) paediatric patients and b) adolescent patients with severe AD. Dupilumab was not used and therefore not included.

Figure S3. Proportion of adult patients with severe AD with at least one prescription of topical therapies (top panel) and systemic therapies (bottom panel).

Figure S4. Proportion of patients with at least one prescription of topical therapy over time in a) paediatric patients and b) adolescent patients, sensitivity analysis.