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ORIGINAL RESEARCH

Treatment Patterns of Atopic Dermatitis Medication in 0–10-Year-Olds: A Nationwide Prescription-Based Study

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ABSTRACT

Introduction: The literature on treatment patterns for paediatric atopic dermatitis (AD) is scarce and is rarely based on real-world data. Using national registers, we sought to establish up-to-date, population-based prevalence estimates, predictors of risk and disease burden and a comprehensive overview of treatment patterns and course for paediatric patients with AD.
Methods: Dispensed prescriptions for the entire Norwegian child population aged 0–10 years from 2014 to 2020 were analysed.
Results: There were 176,458 paediatric patients with AD. Of these, 99.2% received topical corticosteroids, 5.1% received topical calcineurin inhibitors, 37.1% received potent topical corticosteroids and 2.1% received systemic corticosteroids. Of the 59,335 live births in Norway (2014), 14,385 [24.8%; 95% confidence interval (CI) 24.5–25.1] paediatric patients were treated

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for AD before the age of 6 years, and of these, only 934 (6.5%; 95% CI 6.1–6.9) received medication annually for 5 years or more. Compared with girls, 17.9% (95% CI 6.5–27.9) more boys were treated for at least 5 years, receiving 6.4% (95% CI 1.2–11.3) more potent topical corticosteroids and 12.4% (95% CI 6.5–18.0) more were treated for skin infections. Compared with patients with late-onset treatment, 18.9% (95% CI 7.5–29.0) more paediatric patients with early-onset treatment were still receiving treatment at 5 years of age, 15.7% (95% CI 7.1–23.4) more paediatric patients received potent topical corticosteroids and 44.4% (95% CI 36.5–51.2) more paediatric patients were treated for skin infections.

Conclusion: Most paediatric patients were treated for a mild disease for a limited period. Although the prevalence of AD is higher at a younger age, these paediatric patients were the least likely to receive potent topical corticosteroids. Male sex and early-onset AD are associated with and are potential predictors of long-term treatment and treatment of potent topical corticosteroids, antihistamines and skin infections, which may have clinical utility for personalised prognosis, healthcare planning and future AD prevention trials.

Keywords: Child; Atopic dermatitis; Dermatologic agents; Eczema; Emollients; Pharmacoepidemiology; Prescriptions; Topical calcineurin inhibitor; Topical corticosteroids

Key Summary Points

Why carry out this study?

The literature on treatment patterns and disease severity, particularly in paediatric patients under 2 years of age, is sparse and is rarely based on real-world data. Further details on predictors of risk are needed to better facilitate interventions that may halt this epidemic rise of atopic dermatitis in our paediatric populations.

Covering an entire nation of children up to 10 years of age, we sought to establish up-to-date, population-based prevalence estimates and predictors of risk and disease burden and a comprehensive overview of treatment patterns and course for paediatric patients with atopic dermatitis.

What was learned from the study?

We found that male sex and early-onset atopic dermatitis are associated with and are potential predictors of long-term treatment and treatment of potent topical corticosteroids, antihistamines and skin infections.

The highest burden of AD was evident during the first years of life, with a peak prevalence at 1 year of age. We encourage further research to investigate the presumed unmet therapeutic needs of this vulnerable patient group and the applicability of current guidelines, particularly in paediatric patients under 2 years of age.

INTRODUCTION

Atopic dermatitis (AD) causes the most significant burden of disability in the global context of skin diseases and substantial morbidity, including pruritus and reduced personal and family quality of life [1].

Although AD has lagged behind psoriasis in treatment development, a broader therapeutic landscape for AD has emerged in recent years. In the nineteenth century, conventional treatment mainly compromised ointments [2]. Systemic and topical corticosteroids (TCSs) were introduced in the 1950s [3]. Immunosuppressive agents, such as cyclosporine and azathioprine, became available treatment options in the mid-1990s [4]. More recently, second-line systemic options for AD (e.g. JAK inhibitors) have gained a place in therapy but are rarely used and are not approved for young paediatric patients.

The heterogeneity of the clinical picture and disease course of patients with AD indicates a complex reality and uncertain disease trajectories. The literature on treatment patterns and disease severity, particularly in patients under 2 years of age, is sparse [5, 6]. A review by Siegfried et al. [6] revealed limited data on long-term and combination treatment, treatment of severe AD, and systemic corticosteroids in children [6]. In addition, methodological divergence, assessments of AD signs, variations in participants, clinical settings and countries studied were evident.

National health registers from the Nordic countries provide valid, real-world epidemiological data, identifying patients at the individual level on the basis of dispensed prescriptions for disease-specific medications [7–9]. Unique person identifiers and a nationwide sample size provide advanced access to comparative longitudinal data that enable large-scale nationwide cohort studies. We conducted a study covering all paediatric patients who were dispensed prescriptions for AD specific medication up to the age of 10 years from 2014 to 2020 using a novel dataset. The primary objective was to obtain a comprehensive up-to-date overview of prescription-based treatments in paediatric AD. Our secondary objective was to identify treatment patterns and how these relate to long-term and potent topical AD treatment.

METHODS

Ethics Approval and Consent

The observational study was conducted between January 2020 and October 2021. The study was approved by the Regional Committees for Medical and Health Research Ethics Southeast Norway (Ref, REK: 2015/1927) in November 2015 and September 2019, and by the Norwegian Social Science Data Services (NSD) in December 2015. This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the ICMJE requirements on privacy and informed consent. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Study Population

The study covers an annual child population from birth to age 10, consisting of 683,468 patients in 2014 and decreasing to 672,188 in 2020. A total of 59,335 children born in 2014 were followed for 6 years. All children residing in Norway aged 0 to 10 years who had received AD-specific medication [TCSs or topical calcineurin inhibitors (TCIs) or both for external use] were followed up from 1 January 2014 to 31 December 2020.

Registers and Coding Classifications

The nationwide Norwegian Prescription Database (NorPD) holds a unique encrypted personal identifier for all prescriptions dispensed by pharmacies to the Norwegian population, enabling us to track dispensing at the individual level over time.

All dispensed prescriptions for TCSs [Anatomical Therapeutic Chemical Classification (ATC) code D07A], tacrolimus (D11AH01), or pimecrolimus (D11AH02) for external use were extracted from the NorPD according to the ATC/DDD index 2021. In addition, all other prescriptions issued to these patients were extracted. Other medications analysed were combined corticosteroid/antibiotic preparations (D07C), antibiotics for topical use (D06A), antiseptics and disinfectants including hydrogen peroxide (D08AX01), potassium permanganate (D08AX06), dibrompropamidine (D08AC01), systemic antihistamines (R06A), selective immunosuppressants including mycophenolic (L04AA06), calcineurin inhibitors including ciclosporin (L04AD01), other immunosuppressants including azathioprine (L04AX01) and dupilumab (D11AH05), folic acid analogues including methotrexate (L01BA01) and interferons including interferon gamma (L03AB03).

A unique pseudonym replaced the patient number ID. Patient characteristics included age, month and year of birth, date of death, sex, dispense date, generic drug name and ATC codes. Reimbursable prescriptions included codes from the International Statistical Classification of Diseases, Tenth Revision (ICD-10) and the International Classification of Primary Care, version two (ICPC-2) [10].

In Norway, reimbursable prescriptions are issued for chronic diseases. Population statistics were obtained from Statistics Norway.

Algorithm for Identifying Paediatric Patients with Atopic Dermatitis Treatment

Patients were considered to have AD if they met at least one requirement for either criterion, 1 or 2.

1. Criterion 1, on the basis of medical diagnoses: patients with recorded reimbursement prescriptions including associated disease-specific diagnoses of "atopic dermatitis/eczema", recorded as ICD-10 (L20) or ICPC-2 (S87).
2. Criterion 2, on the basis of disease-specific medication dispensed: patients with non-reimbursable prescriptions (no AD diagnosis as in criterion **1)** were considered to have AD if the child, within 1 year, the child had either:

- ≥ two prescriptions of TCS (minimum 14 days apart)
- ≥ one prescription of TCI

3. *Non-AD criteria*: Patients classified under criterion 2, with co-occurring ICD-10/ICPC-2 skin diagnoses (which could lead to identical treatments) or co-occurring skin disease-specific medications (primarily prescribed for other conditions), were not considered to have AD.

The online Supplementary Material provides further explanations of the algorithm employed.

Categorising Paediatric Patients based on the Potency of TCSs

Patients were categorised into three levels on the basis of the highest potency of TCS treatment received (with or without TCIs, systemic treatment including corticosteroids, immunosuppressants, calcineurin inhibitors, folic acid analogues and interferons). Level 1 was defined as patients treated exclusively with weak TCSs (group I). Level 2 was defined as moderate TCSs (group II). Level 3 was defined as potent or very potent TCSs (group III/IV). A more potent TCS class overruled a less potent one.

Statistical Analysis

We used Poisson regression based on the algorithm to calculate the 1-year prevalence of dispensed drugs with a 95% confidence interval (CI). Data were stratified by age and sex, early and late treatment initiation, and years of treatment. The dataset was adjusted for sex differences within the population. Descriptive statistics were reported as mean, standard deviation (SD) or median for continuous variables, and as frequency (per cent) for categorical variables. A chi-square test tested the differences between rates. $P < 0.05$ (2-sided test) was considered statistically significant.

The annual prevalence (based on age) was measured as the number of individuals receiving at least one prescription of AD medication per age. Continuous assessments of the same individuals over time can occur. The dominator from Statistics Norway was presented by sex and age on the basis of the midyear Norwegian population each year.

The 2014 birth cohort was stratified by index age (baseline age), defined as the age of exposure (dispensed prescription of AD medication). Patients with an index age of 0–6 months were set as the reference group to stratify and assess the treatment pattern and predictor of severity and long-term AD treatment. The 2014 birth cohort was divided into four cohorts (6-month periods) according to index age. Patients with an early index age (0–6 months) were compared with patients with a late index age

(18–24 months). Age- and sex-specific analyses and analyses of the strength of TCSs dispensed were performed.

The total number of years of AD treatment were analysed to assess the duration of treatment. We also analysed the number of patients receiving regular AD treatment (persistence) with a maximum interval of 1 year between redemptions for at least 2 years, from index age to 6 years of age.

Days of follow-up were defined as the period between indexation (index age) and the first date of emigration, death or cut-off date of the NorPD data (31 December 2020), whichever occurred first. Data were analysed using Stata/MP software (version 17.0; StataCorp LLP).

RESULTS

Prescription and Patient Selection

From 2014 to 2020, 176,458 patients were treated for AD according to the algorithm. Overall, 90.7% (160,022) of the included patients had a physician-issued reimbursable prescription and associated AD diagnoses (criterion 1). There were 589,687 topical AD medication prescriptions (317,593 dispensed to 92,436 boys and 262,094 to 84,022 girls). The median observation period per child was 38.2 months (interquartile range 16.0; 60.0).

Treatment Patterns in Paediatric Patients Aged 0–10 years, (Table 1)

The period prevalence for all ages combined was 6.7% (95% CI 6.7–6.8). The statistics displayed a significant preponderance of boys receiving AD treatment. There were no significant differences between the sexes after the age of 4. The average prescriptions dispensed per year per child, and the mean number of grams of prescribed topical treatment indicated a steady decline with increasing age.

Almost all patients were dispensed TCSs. Only 1435 patients (0.8%; 95% CI 0.8–0.9) were prescribed TCIs as single therapy (excluding other topical therapies). Only a minority were prescribed very potent (group IV) TCSs. The number of patients receiving potent TCSs (group III) and TCIs increased with age.

Patients were categorised into three levels on the basis of the highest potency of TCSs received. Overall, 107,795 (61.1%; 95% CI 60.9–61.3) received only weak or moderately potent TCSs. In addition, 21,610 (12.2%; 95% CI 12.1–12.4) patients received potent or very potent TCSs without previously having received weak or moderately potent TCSs.

Overall, dispensed systemic immunosuppressant was marginal: azathioprine (n = 131), cyclosporine (n = 186), interferon gamma (n = 0), methotrexate (n = 1), mycophenolate mofetil (n = 70), baricitinib (n = 0) and dupilumab (n = 2).

Characteristics of the 2014 Birth Cohort, (Table 2)

Of the 59,335 live births in Norway (2014), 14,385 (24.8%; 95% CI 24.5–25.1) patients were treated for AD before the age of 6 years. Of these, 934 patients (6.5%; 95% CI 6.1–6.9) received AD medication annually for 5 years (or more).

The analysis revealed (387/6,658 girls compared with 547/7727 boys) 17.9% (95% CI 6.5–27.9) more boys than girls received at least 5 years of dispensed AD treatment (or more). However, there was no statistically significant difference between the sexes in terms of persistence (regular redemption of AD treatment). Accordingly, (2428/6658 girls compared with 3010/7727 boys) 6.4% (95% CI 1.2–11.3) more boys received potent/very potent TCSs than girls. In addition, (2428/6658 girls compared with 3010/7727 boys) 12.4% (95% CI 6.5–18.0) more boys were treated for skin infections (at least one of the following: weak TCSs in combination with antibiotics or topical antibiotics, antiseptics or disinfectants). We found that (1956/6658 girls compared with 2412 /7727 boys) 5.9% (95% CI 0.1–11.3) more boys than girls received antihistamines before the age of 6 and (122 /6658 girls compared with 195/7727 boys) 27.4% (95% CI 9.0–42.1) more boys received systemic corticosteroids.

Table 1 Demographics, treatment category and clinical characteristics of the 176,458 patients with AD, by ages 0–10, years 2014–2020

Patient characteristics by age (per cent of total)[a]	**Age 0, *n* = 45,281 (25.7%)**	**Age 1, *n* = 50,055 (28.4%)**	**Age 2, *n* = 39,627 (22.5%)**	**Age 3, *n* = 31,319 (17.7%)**	**Age 4, *n* = 27,296 (15.5%)**	**Age 5, *n* = 24,723 (14.0%)**
Demographics						
Norwegian population (2014–2020)	404,632	415,257	424,007	431,976	438,031	442,587
Prevalence, per cent (95% CI)	11.1(11.1–11.3)	12.1(11.9–12.2)	9.3 (9.3–9.4)	7.3 (7.2–7.3)	6.2 (6.2–6.3)	5.6 (5.5–5.7)
Age, years, mean ± SD; median	0.6 ± 0.2; 0.5	1.5 ± 0.3; 1.4	2.4 ± 0.3; 2.4	3.4 ± 0.3; 3.4	4.5 ± 0.3; 4.4	5.5 ± 0.3; 5.4
Sex, male	26,490 (58.5)	27,624 (55.2)	21,368 (53.9)	16,550 (52.8)	14,122 (51.7)	12,472 (50.5)
Total received prescriptions of TCS and TCI. Mean ± SD; median	2.1 ± 1.7; 1.0	1.9 ± 1.6; 1.0	1.9 ± 1.6; 1.0	1.8 ± 1.6; 1.0	1.8 ± 1.6; 1.0	1.8 ± 1.6; 1.0
Total gram of TCSs and TCIs. Mean ± SD; median	127.0 ± 134.7; 100.0	123.1 ± 134.8; 100.0	122.9 ± 134.9; 100.0	123.4 ± 140.2; 100.0	122.5 ± 146.2; 100.0	122.2 ± 148.1; 100.0
Number of dispensed prescriptions of TCSs or TCIs per age						
≥ 2	22,427 (49.5)	22,738 (45.4)	16,888 (42.6)	12,850 (41.0)	10,675 (39.1)	9425 (38.1)
≥ 3	10,240 (22.6)	9523 (19.0)	7179 (18.1)	5223 (16.7)	4406 (16.1)	3714 (15.0)
Annual combination therapy with ≥ 2 distinct treatments of TCSs or TCIs[c]	15,587 (34.4)	14,426 (28.8)	10,725 (27.1)	7942 (25.4)	6606 (24.2)	5783 (23.4)
TCSs						
Any potency	45,182 (99.8)	49,767 (99.4)	39,165 (98.8)	30,917 (98.7)	26,888 (98.5)	24,345 (98.5)
Weak (group I)	29,009 (64.1)	24,907 (49.8)	16,499 (41.6)	11,866 (37.9)	9498 (34.8)	8106 (32.8)

Table 1 continued

Patient characteristics by age (per cent of total)[a]	Age 0, *n* = 45,281 (25.7%)	Age 1, *n* = 50,055 (28.4%)	Age 2, *n* = 39,627 (22.5%)	Age 3, *n* = 31,319 (17.7%)	Age 4, *n* = 27,296 (15.5%)	Age 5, *n* = 24,723 (14.0%)
Moderately potent (group II)	25,163 (55.6)	28,699 (57.3)	22,729 (57.4)	17,270 (55.1)	14,539 (53.3)	12,696 (51.4)
Potent (group III)	8498 (18.8)	11,529 (23.0)	10,884 (27.5)	9639 (30.8)	9137 (33.5)	8833 (35.7)
Very potent (group IV)	171 (0.4)	340 (0.7)	479 (1.2)	532 (1.7)	636 (2.3)	680 (2.8)
TCIs	748 (1.7)	1156 (2.3)	1528 (3.9)	1292 (4.1)	1237 (4.5)	1140 (4.6)
Highest TCSs potency received[d]						
1. Weak (group I)	15,421 (34.0)	13,851 (27.7)	9320 (23.3)	6963 (22.2)	5734 (21.0)	4932 (20.0)
2. Moderately potent (group II)	21,230 (46.9)	24,427 (48.8)	19,062 (48.1)	14,310 (45.7)	11,936 (43.7)	10,417 (42.1)
3. Potent/Very potent (group III/IV)	8630 (19.1)	11,777 (23.5)	11,245 (28.4)	10,046 (32.1)	9626 (35.3)	9374 (37.9)
Weak TCSs in combinations with antibiotics, topical antibiotics, topical antiseptics and disinfectants[e]	5527 (12.2)	4979 (10.0)	3869 (9.8)	2902 (9.3)	2597 (9.5)	2398 (9.7)
Systemic treatments						
Antihistamines[f]	4240 (9.4)	9593 (19.2)	9186 (23.2)	8044 (25.7)	7623 (27.9)	5225 (27.9)
Corticosteroids[g]	283 (0.6)	754 (1.5)	522 (1.3)	409 (1.3)	338 (1.2)	317 (1.3)
Antineoplastic and immunomodulating agents[h]	8 (0.0)	16 (0.0)	23 (0.1)	10 (0.0)	20 (0.1)	25 (0.1)

Table 1 continued

Patient characteristics by age (per cent of total)[a]	Age 6, *n* = 22,572 (12.8%)	Age 7, *n* = 21,153 (12.0%)	Age 8, *n* = 21,153 (11.7%)	Age 9, *n* = 20,137 (11.4%)	Age 10, *n* = 19,775 (11.2%)	Total, *n* = 176,458 (100.0%)
Demographics						
Norwegian population (2014–2020)	445,160	447,933	447,508	446,809	444,104	–
Prevalence, per cent (95% CI)	5.1 (5.0–5.1)	4.7 (4.7–4.8)	4.6 (4.5–4.7)	4.5 (4.4–4.6)	4.5 (4.4–4.5)	–
Age, years, mean ± SD; median	6.5 ± 0.3; 6.4	7.5 ± 0.3; 7.4	8.5 ± 0.3; 8.4	9.5 ± 0.3; 9.3	10.5 ± 0.3; 10.4	–
Sex, male	11,117 (49,2)	19,282 (48.6)	10,193 (49.5)	9969 (49.5)	9856 (49.8)	92,436 (52.7)
Total received prescriptions of TCS and TCI. Mean ± SD; median	1.7 ± 1.6; 1.0	1.7 ± 1.5; 1.0	1.7 ± 1.5; 1.0	1.7 ± 1.5; 1.0	1.7 ± 1.5; 1.0	–
Total gram of TCSs and TCIs. Mean ± SD; median	119.7.1 ± 151.0; 100.0	119.4 ± 145.5; 100.0	120.0 ± 146.1; 100.0	120.4 ± 142.9; 100.0	121.6 ± 146.1; 100.0	–
Number of dispensed prescriptions of TCSs or TCIs per age						
≥ 2	8349 (37.0)	7810 (36.9)	7519 (36.5)	7475 (37.1)	7294 (36.9)	23,476 (38.8)
≥ 3	3223 (14.3)	3007 (14.2)	2935 (14.2)	2871 (14.3)	2867 (14.5)	8696 (14,4)
Annual combination therapy with ≥ 2 distinct treatments of TCSs or TCIs[c]	5061 (22.4)	4791 (22.6)	4576 (22.2)	4518 (22.4)	4427 (22.4)	45,749 (25.9)
TCSs						
Any potency	22,185 (98.3)	20,758 (98.1)	20,187 (98.0)	19,694 (97.8)	19,284 (97.5)	175,023 (99.2)
Weak (group I)	6893 (30.5)	6062 (28.7)	5708 (27.7)	5447 (27.1)	5041 (25.5)	91,051 (51.6)
Moderately potent (group II)	11,296 (50.0)	10,269 (48.6)	9688 (47.0)	9077 (45.1)	8624 (43.6)	108,373 (61.4)
Potent (group III)	8508 (37.7)	8548 (40.4)	8708 (42.3)	8926 (44.3)	9146 (46.3)	65,520 (37.1)
Very potent (group IV)	779 (3.5)	797 (3.8)	799 (3.9)	863 (4.3)	953 (4.8)	5754 (3.3)

Table 1 continued

Patient characteristics by age (per cent of total)[a]	Age 0, *n* = 45,281 (25.7%)	Age 1, *n* = 50,055 (28.4%)	Age 2, *n* = 39,627 (22.5%)	Age 3, *n* = 31,319 (17.7%)	Age 4, *n* = 27,296 (15.5%)	Age 5, *n* = 24,723 (14.0%)
TCIs	1006 (4.5)	1057 (5.0)	1072 (5.2)	1119 (5.6)	1173 (5.9)	9044 (5.1)
Highest TCSs potency received[d]						
1. Weak (group I)	4308 (19.1)	3800 (18.0)	3643 (17.7)	3481 (17.3)	3292 (16.7)	31,750 (18.0)
2. Moderately potent (group II)	9162 (40.6)	8234 (38.9)	7689 (37.3)	7123 (35.4)	6681 (33.8)	76,045 (43.1)
3. Potent/Very potent (group III/IV)	9102 (40.3)	9119 (43.1)	9275 (45.0)	9533 (47.3)	9802 (49.6)	68,663 (38.9)
Weak TCSs in combinations with antibiotics, topical antibiotics, topical antiseptics and disinfectants[e]	2031 (9.0)	1931 (9.1)	1760 (8.5)	1727 (8.6)	1604 (8.1)	35,106 (19.9)
Systemic treatments						
Antihistamines[f]	7289 (29.3)	6494 (30.7)	6619 (32.2)	6715 (33.4)	6751 (34.1)	51,844 (29.4)
Corticosteroids[g]	279 (1.2)	281 (1.3)	299 (1.5)	354 (1.8)	327 (1.7)	3614 (2.1)
Antineoplastic and immunomodulating agents[h]	25 (0.1)	34 (0.2)	39 (0.2)	44 (0.2)	52 (0.3)	203 (0.1)

All values are expressed in *N* (percent) unless otherwise specified. Percentages are calculated according to total number of patients (*N*) in the corresponding age group

[a]Continuous assessments of the same individuals over time can occur. Age is defined as the time medication was dispensed

[b]Annually dispensed topical treatment from two groups of TCSs or TCS(s) combined with TCI(s)

[c]Patients were categorised into three levels on the basis of the highest potency of TCS treatment received during the observation period [with or without receiving TCI(s), systemic corticosteroids, azathioprine, cyclosporine A, methotrexate, mycophenolate mofetil, interferon gamma or intravenous immunoglobulin]. Level 1 was defined as the exclusive use of weak TCS (group I). Level 2 was defined as moderate TCS (group II). Level 3 was defined as potent or very potent TCS (group III/IV). A more potent TCS class overruled a less potent one

[d]"Corticosteroids, combinations of antibiotics (D07C)", "Antibiotics for topical use (D06A)" and "Antiseptics and disinfectants including hydrogen peroxide (D08XC01), potassium permanganate (D08AX06) and dibrompropamidine (D08AC01)" prescribed at the same age the patient received TCSs or TCIs or both

[e]"Systemic antihistamines (R06A) – Comprises plain and combined antihistamine preparations for systemic use" prescribed at the same age the patient received TCS(s) or TCI(s) or both

[f]"Systemic corticosteroids (H02A) – Only plain preparations are classified in this group" – prescribed at the same age the patient received TCS(s) or TCI(s) or both

[g]"Selective immunosuppressants including mycophenolic acid (L04AA06)", "Calcineurin inhibitors including ciclosporin (L04AD01)", "Other immunosuppressants including azathioprine (L04AX01) and dupilumab (D11AH05)", "Folic acid analogues including methotrexate (L01BA01)" and "Interferons including interferon gamma (L03AB03)" – prescribed at the same age the patient received TCS(s) or TCI(s) or both

Table 2 Demographics, treatment category and clinical characteristics of patients with AD born in 2014, followed until the age of 6 (on the basis of the 59,335 0-year-olds born in 2014)

Patient characteristics	Total, *n* = 14,385 (100.0%)	Female, *n* = 6658 (46.3%)	Male, *n* = 7727 (53.7%)	Index age 0–6 months, *n* = 2505 (17.4%)	Index age 6–12 months, *n* = 2953 (20.5%)	Index age 12–18 months, *n* = 2055 (14.3%)	Index age 18–24 months, *n* = 1799 (12.5%)
Demographics							
Age, years, mean ± SD; median[a]	2.6 ± 1.7; 2.3	2.8 ± 1.7; 2.5	2.5 ± 1.6; 2.2	1.9 ± 1.7; 1.4	2.2 ± 1.6; 1.7	2.5 ± 1.4; 1.5	2.8 ± 1.3; 2.3
Sex, male	7,727 (53.7)	(–)	(–)	1575 (62.9)	1701 (57.6)	1103 (53.7)	920 (51.1)
Total years receiving TCSs or TCIs							
1 year	6357 (44.2)	2968 (44.6)	3389 (43.9)	717 (28.6)	868 (29.4)	892 (43.4)	727 (40.4)
2 years	4047 (28.1)	1929 (29.0)	2118 (27.4)	620 (24.8)	892 (30.2)	610 (29.7)	553 (30.7)
3 years	2004 (13.9)	925 (13.9)	1079 (14.0)	451 (18.0)	540 (18.3)	283 (13.8)	303 (16.8)
4 years	1043 (7.3)	449 (6.7)	594 (7.7)	314 (12.5)	311 (10.5)	169 (8.2)	128 (7.1)
5 years	592 (4.1)	247 (3.7)	345 (4.5)	(–)	(–)	(–)	(–)
6 years	342 (2.4)	140 (2.1)	202 (2.6)	(–)	(–)	(–)	(–)
Persistence: regularly received prescriptions of TCS or TCI[b]	1857 (12.9)	825 (12.4)	1032 (13.4)	473 (18.9)	319 (10.8)	263 (12.8)	205 (11.4)
Received TCSs at age 5	3786 (26.3)	1907 (28.6)	1879 (24.3)	596 (23.8)	618 (20.9)	425 (20.7)	347 (19.3)
Received group III/IV TCSs at age 5	5438 (37.8)	2428 (36.5)	3010 (40.0)	1088 (43.4)	1098 (37.2)	790 (38.4)	659 (36.6)
Total received prescriptions of TCS and TCI per age. Mean ± SD; median	1.8 ± 1.4; 1.0	1.7 ± 1.3; 1.0	1.9 ± 1.5; 1.0	2.8 ± 2.2; 2.0	1.6 ± 1.0; 1.0	1.9 ± 1.4; 2.0	1.4 ± 0.8; 1.0
Total gram of TCSs and TCIs per age. Mean ± SD; median	106.9 ± 110.8; 90.0	99.1 ± 100.0; 80.0	113.6 ± 118.9; 100.0	169.0 ± 175.4; 100.0	88.6 ± 82.6; 60.0	111.0 ± 112.6; 100.0	82.0 ± 65.0; 60.0

Table 2 continued

Patient characteristics	Total, *n* = 14,385 (100.0%)	Female, *n* = 6658 (46.3%)	Male, *n* = 7727 (53.7%)	Index age 0–6 months, *n* = 2505 (17.4%)	Index age 6–12 months, *n* = 2953 (20.5%)	Index age 12–18 months, *n* = 2055 (14.3%)	Index age 18–24 months, *n* = 1799 (12.5%)
Total received prescriptions of TCS or TCI per age							
≥ 2 treatments	5820 (40.5)	2564 (38.5)	3256 (42.1)	1540 (61.5)	1154 (39.1)	892 (43.4)	555 (30.9)
≥ 3 treatments	2359 (16.4)	977 (14.7)	1382 (17.8)	877 (35.0)	452 (15.3)	361 (17.6)	171 (9.5)
Highest potency of TCSs received[d]							
1. Weak (group I)	2458 (17.1)	1167 (17.5)	1291 (16.7)	360 (14.4)	490 (16.6)	379 (18.4)	310 (17.2)
2. Moderately potent (group II)	6489 (45.1)	3063 (46.0)	3426 (44.3)	1057 (42.2)	1365 (46.2)	886 (43.1)	830 (46.1)
3. Potent/very potent (group III/IV)	5438 (37.8)	2428 (36.5)	3010 (39.0)	1088 (43.4)	1098 (37.2)	790 (38.4)	659 (36.6)
TCIs	698 (4.9)	310 (4.7)	388 (5.0)	174 (7.0)	140 (4.7)	93 (4.5)	79 (4.4)
Weak TCSs in combination with antibiotics, topical antibiotics, topical antiseptics and disinfectants[)]	2791 (19.4)	1204 (18.1)	1587 (21.8)	776 (31.0)	667 (22.6)	379 (18.4)	310 (17.2)
Systemic treatments							
Antihistamines[f]	4368 (30.4)	1956 (29.4)	2412 (33.1)	984 (39.3)	902 (30.6)	620 (30.2)	559 (31.1)
Corticosteroids[g]	317 (2.2)	122 (1.8)	195 (2.5)	68 (2.7)	69 (2.3)	56 (2.7)	35 (2.0)

Table 2 continued

Patient characteristics	Total, *n* = 14,385 (100.0%)	Female, *n* = 6658 (46.3%)	Male, *n* = 7727 (53.7%)	Index age 0–6 months, *n* = 2505 (17.4%)	Index age 6–12 months, *n* = 2953 (20.5%)	Index age 12–18 months, *n* = 2055 (14.3%)	Index age 18–24 months, *n* = 1799 (12.5%)
Antineoplastic and immunomodulating agents[h]	12 (0.1)	8 (0.1)	4 (0.1)	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.1)

Unless otherwise specified, all values are expressed in *N* (percentages)

Percentages are calculated according to total patients *(N)* in the corresponding age group

The index age for patients with 5 and 6 years of treatment could not be determined owing to the short follow-up period

[a]Age at the time medication was dispensed

[b]The number of patients receiving regular AD treatment (persistence) from the index age until the age of 6, for at least 2 years with a maximum 1-year gap between redemptions

[c]Annually dispensed topical treatment from two groups of TCSs or TCS(s) in combination with TCI(s)

[d]Patients were categorised into three levels on the basis of the highest potency of TCS treatment received during the observation period [with or without receiving TCI(s), systemic corticosteroids, azathioprine, cyclosporine A, methotrexate, mycophenolate mofetil, interferon gamma or intravenous immunoglobulin]. Level 1 was defined as the exclusive use of weak TCS (group I). Level 2 was defined as moderate TCS (group II). Level 3 was defined as potent or very potent TCS (group III/IV). A more potent TCS class overruled a less potent one

[e]"Corticosteroids, combinations of antibiotics (D07C)", "Antibiotics for topical use (D06A)" and "Antiseptics and disinfectants including hydrogen peroxide (D08AX01), potassium permanganate (D08AX06), dibrompropamidine (D08AC01)" prescribed at the same age the patient received TCSs or TCIs or both

[f]"Systemic antihistamines (R06A) – Comprise plain and combined antihistamine preparations for systemic use" prescribed at the same age the patient received TCS(s) or TCI(s) or both

[g]"Systemic corticosteroids (H02A) – Only plain preparations are classified in this group" – prescribed at the same age the patient received TCS(s) or TCI(s) or both

[h]"Selective immunosuppressants including mycophenolic acid (L04AA06)", 'Calcineurin inhibitors including ciclosporin (L04AD01)", 'Other immunosuppressants including azathioprine (L04AX01) and dupilumab (D11AH05)", 'Folic acid analogues including methotrexate (L01BA01)" and 'Interferons including interferon gamma (L03AB03)" – prescribed at the same age the patient received TCS(s) or TCI(s) or both

Overall, (596/2505 early index age compared with 347/1799 late index age) 18.9% (95% CI 7.5–29.0) more patients with an early index age (0–6 months) were still receiving AD treatment at 5 years of age compared with patients with a late index age (18–24 months). In terms of persistence, (473/2505 early index age compared with 205/1799 late index age) 39.7% (95% CI 28.9–48.8) more patients with an early index age received regular medication compared with patients with a late index age.

Compared with patients with a late index age, (1088/2505 early index age compared with 659 /1799 late index age) 15.7% (95% CI 7.1–23.4) more patients with early index age received potent or very potent TCSs. When comparing patients with an early and late index age, (877/2505 early index age compared with 171/1799 late index age) 72.8% (95% CI 68.0–77.0) more patients with an early index age patients received three (or more) types of topical treatment (TCSs or TCSs combined with TCIs) per year.

Moreover, (776/2505 early index age compared with 310/1799 late index age) 44.4% (95% CI 36.5–51.2) more patients with an early compared with a late index age were treated for skin infections before age 6. Patients with an early index age received (174/2505 early index age compared with 79 /1799 late index age) 37.1% (95% CI 18.0–51.8) more TCIs than patients with a late index age.

When we analysed antihistamines received before the age of 6, we found (964/2505 early index age compared with 559/1799 late index age) 20.9% (95% CI 12.2–28.7) more patients with an early index age than a late index age. We also found an increased rate of prescribed systemic corticosteroids in patients with an early index age. However, the results were not statistically significant.

DISCUSSION

Globally, to our knowledge, this is the only nationwide study to quantify paediatric AD disease-specific prescriptions and provide a real-world overview of prevalence, treatment patterns, course and predictors, including subgroup characteristics.

The prevalence of Norwegian children receiving AD treatment has decreased with age, ranging from 11% at age 1 to under 5% at age 10 (Table 1). The decline was expected on the basis of the commonly observed disease course of early AD onset, followed by improvement in adolescence. In a 2020 US claims data analysis of AD paediatric patients, Paller et al. [5] observed that most patients receiving AD treatment were 0–1 years old. This study confirms their findings regarding the high prevalence of early-onset treatment.

In the 2014 birth cohort, most patients received short-term treatment of TCSs/TCIs. Around 7% of the patients received AD medication annually for 5 years (or longer) and merely one in four patients were still receiving AD treatment at age 5. In a review of 45 studies involving 110,651 children, the authors found that 80% of childhood AD did not persist by age 8 [11], which underlines our findings.

A substantial proportion of young patients with flexural and facial skin involvement may explain why approximately 80% of them, in the first year of life, received weak or moderately potent TCSs as the highest potency, dropping to 50% by age 10. This finding, together with the general short-term need for AD treatment, is consistent with current knowledge that AD is a mild disease in the majority of cases [5, 12–14].

The number of TCI prescriptions increased with age, accompanied by more potent TCSs, confirming the findings in the US study. A minority of patients received very potent TCSs or systemic therapy. Four out of ten patients received (at least once before the age of 10) potent or very potent TCSs, indicating moderate to severe disease. Since AD is not treated with systemic therapy alone, the prevalence of severe AD before the age of 6 is estimated to be 9.2% in the 2014 birth cohort (according to the proxy). A recent study by Silverberg et al. estimated the proportion of severe AD in 18 countries to be 3.1%-11.0% (except Israel; 24.9%) in children under 6 years of age [15]. These paediatric patients with severe and complex disease are potential candidates for future systemic medication.

Although AD is a chronic disease, the age of onset and disease expression varies across individuals and within seasons. In addition, AD often runs within families. Although it is not recommended, familial sharing of prescribed medication does occur. Moreover, patients may fill their prescriptions just before their birthday, which means they might have received sufficient medication for the following year. If we account for the age of onset (of AD treatment) and frequency of redemption (at least every second year), the proportion of patients receiving regular AD treatment was roughly 13%, which could reinforce the assumption of generally poor adherence in patients with AD [16].

In the 2014 birth cohort, nearly one in five patients received early-onset AD treatment (index age: 0–6 months). We suggest that early-onset AD treatment is associated with significantly severe AD patterns. Overall, patients with early-onset AD treatment were treated with more TCSs and TCIs (higher number of prescriptions and number of grams), they received prescriptions more regularly with more potent (or very potent) TCSs and more were treated for skin infections. In addition, significantly more patients with early-onset AD treatment were still receiving AD treatment at age 5 compared with patients with late-onset AD treatment (index age: 18–24 months). A Danish study of AD disease severity in paediatric patients found that early-onset AD (< 1 year of age) was associated with more severe disease [17]. Previous research suggests that patients with early-onset AD have a significantly higher frequency of filaggrin loss-of-function mutations, increased AD duration and hospitalisation, inadequate disease control and increased persistence [18, 19]. All these studies are consistent with our findings.

The highest burden of AD was evident during the first years of life, with a peak prevalence at 1 year of age. A Danish study [20] concluded that children with AD had the highest disease burden in the second year of life. In the present study, the mean annual number of grams of AD medication per child hardly decreased with age. However, more medication was prescribed to the youngest patients relative to body size. Moreover, the highest annual number of prescriptions and the highest number of combination treatments and skin infection treatments were associated with early onset AD treatment, confirming our findings that AD is a more common and severe condition in the first years of life [20]. Although the prevalence and burden of AD is substantially higher at a younger age, these patients were the least likely to receive potent TCSs [5]. Overall, treatment with more potent TCSs could lead to more rapid skin improvement and disease control, ultimately resulting in fewer TCSs being used overall and fewer physician visits and prescriptions (implying it is also more cost effective) [21–26]. Conclusively, guidelines for the potency of medications adapted to the severity of the disease and the anatomical site of the application according to age, especially in patients under 2 years of age, need to be more specific [27]. It could enhance the potential to treat young paediatric patients more effectively and safely.

The preponderance of boys receiving early-age AD treatment reflects previous research [28–30]. A recent Norwegian study showed that the male sex was predictive of high transepidermal water loss at 3 months of age [31]. According to another recent review, the point prevalence of AD in girls was 24% compared with 35% in boys before age 1. In school-aged children, the prevalence was around 11% in girls and 8% in boys [32]. In addition, the Danish study concluded that disease severity was associated with the male sex, which is consistent with our findings that increased prescription of potent/very potent TCSs are associated with a prolonged disease course and increased risk for skin infections.

There are notable discrepancies in the literature regarding paediatric patients treated with TCIs. In a review by Siegfried et al., TCI treatment ranged from 0% to 52% [6]. Accordingly, we found that only 5% of the patients received TCIs, consistent with Paller et al. The 2005/2006 warnings about the long-term effects (i.e. lymphoma) may have led to less frequent prescribing of TCIs [33]. In addition, the preparations are expensive and not approved as a reimbursement prescription (although individual reimbursement can be granted).

While mainly prescribed for allergies, antihistamines were commonly prescribed for AD. The proportion of dispensed antihistamines was significantly higher in patients with early-onset AD treatment than late-onset treatment. Notably, early-onset AD is associated with a higher risk of seasonal allergies and asthma than late-onset AD [34]. However, another observational cohort study suggests that early-onset and early-resolving AD are not associated with the development of allergic disease at 3 years of age [35]. The published literature on early-onset and early-resolving AD is scarce, and the heterogeneity of AD needs further investigation.

Although systemic corticosteroids can lead to rapid clearing of AD, their use is limited owing to the side effects and the risk of severe rebound flare when discontinued [36]. The total number of systemic corticosteroids administered in the study population was low, close to 2% (a maximum estimate considering the number of prescriptions without ICD/ICPC coding). Furthermore, the high number of dispensed systemic corticosteroids is probably determined by the burden of comorbid asthma and hay fever. A more reasonable estimate would be around 1%, which contrasts with the high consumption (24%) in US paediatric patients recorded by Paller et al. As the course and severity of paediatric AD are likely to be similar in the USA and Norway, this result suggests that non-medical factors (e.g. extent of private health care and treatment traditions) play an essential role in clinical decisions.

In the US database study, prescribed systemic treatment, including immunosuppressants, calcineurin inhibitors, folic acid analogues and interferons ranged from 0.0% in patients aged 1 year to 0.3% in patients aged 10 years [5]. Such marginal prescribing might be rooted in the lack of robust long-term data on the effects of these drugs on paediatric patients [37].

Strengths and Limitations

The large sample size of the longitudinal individual-based novel dataset for the entire population of Norwegian children under the age of 11 ensures robustness with high significance and generalisability. Another strength is that children from all social strata are included in the study, as the social welfare system in Norway is free of charge for paediatric patients. Moreover, Norway has a high number of practising physicians who provide accessible healthcare throughout the country. Another major strength is the NorPD's complete coverage of all prescriptions dispensed by pharmacies to the Norwegian population, including all outpatients.

Topical hydrocortisone 1% is available over the counter and could affect sensitivity. However, the Norwegian welfare system provides reimbursement prescriptions (free of charge) for paediatric patients with chronic diseases such as AD. Consequently, an over-the-counter purchase is a more expensive option, and the analysed sample is expected to be representative [38]. Finally, although this study is performed retrospectively, the actual data are collected in a prospective fashion independent of the study itself, thus eliminating some of the inherent biases commonly identified for traditional retrospective studies (e.g. recall bias, information bias, interview bias, data collection biases and primary non-compliance [39].

Several potential limitations should be discussed. Firstly, the prevalence of AD treatment is closely linked with outcome definitions and should be interpreted cautiously. Secondly, the correspondence between prescriptions dispensed and actual medication use is unknown and should be considered a maximum estimate. Conversely, the time between the first and last prescription received should be interpreted as a minimum estimate, as the time course of administration is unknown. Thirdly, TCSs are prescribed for a broad group of skin conditions, perhaps distorting the true picture of AD drug treatment in the study population [7, 8]. Although often used as the gold standard in studies, physician-recorded diagnoses may lead to incorrect coding and interfere with the prescribing proportions' denominators. This study's algorithm was predominantly based on physician-recorded diagnoses (criterion one). The criterion two (algorithm) was minimised to only 9.3% of the patients included. A validation study [7] found that two or more annual

prescriptions of TCS yielded a sensitivity value of 40% and a positive predictive value of 60%. However, the non-AD criteria (criterion 3) increased the positive predictive value. Fourthly, 1.0% of prescriptions lacked identification numbers and were excluded. However, AD is defined as a chronic disease, and a paediatric AD patient would presumably have received prior or subsequent medical treatment. It is therefore conceivable that the majority of the excluded prescriptions belong to the included patients.

Finally, this study does not address carbamide (urea) creams. Dupilumab was licensed in 2020 for patients over 12 years of age, and crisaborole was not licenced AD treatment during the study period. Moreover, this study does not include phototherapy and climate therapy under the auspices of the public health service.

CONCLUSIONS

In this nationwide real-world registry study, all topical and systemic medications dispensed were documented up to the age of 10 years.

We found that AD was a mild and short-term condition in most paediatric patients. Only a minority of the patients received potent TCSs. Male sex and early-onset AD are associated with, and are potential predictors of, long-term treatment and treatment of potent topical corticosteroids, antihistamines and skin infections. Systemic treatments such as corticosteroids, immunosuppressants, calcineurin inhibitors, folic acid analogues and interferons were marginally prescribed.

There is a need for real-world global knowledge transfer, learning from longitudinal existing treatment patterns in paediatric patients and how differences in treatment patterns are associated with the subsequent prevalence and course of AD in older patients. Although the recommended clinical guidelines were followed, we encourage further research to investigate the presumed unmet therapeutic needs of this vulnerable patient group and the applicability of current guidelines, particularly in paediatric patients under 2 years of age.

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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