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ORIGINAL ARTICLE

Treatment and referral patterns of patients with atopic dermatitis from the Danish primary care system to the tertiary care system

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Abstract

Background: Patients with atopic dermatitis (AD) are mostly managed by general practitioners (GPs) and practicing dermatologists (PDs) in Denmark. In cases of severe and refractory AD, the primary physician can refer the patient to a specialised dermatology department.

Objectives: Aim of the study was to investigate treatment at the time of referral to a specialised dermatology department and the cause stated by the GP in a Danish cohort of AD patients referred to the Department of Dermatology, Aarhus University Hospital from 2019 to 2021.

Methods: One hundred and thirty cases were randomly selected via diagnosis codes for AD. Information regarding the cause for referral and treatment given at time of referral was obtained from medical records. 18 cases were excluded due to missing referral in the patients' medical records, other diagnosis than AD or treatment initiation before 2019. The final cohort consisted of 112 cases. Differences between patients referred from GP and PD were analysed with Fisher's exact test.

Results: Most cases were referred by PDs (45.5%) and GPs (24.1%). GPs primarily referred due to acute flare-ups in need of treatment (40.7%), and PDs due to lacking disease control (64.7%), (p-values < 0.0018). GPs generally included more descriptive information in their referrals than PDs, however, only the difference in mentioning sleep disturbance was significant (p-value $= 0.0144$). Topical corticosteroids were the preferred treatments before referral regardless of the referring doctor, with no statistical differences. Topical calcineurin inhibitors were significantly more used among PD-referred patients compared to GP-referred patients (p-value $= 0.0018$).

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Systemic therapy was initiated in 45 patients (40.2%) at the tertiary hospital with no differences between referral from either GPs or PDs.

Conclusions: The study identified few differences in the referral pattern of AD to a tertiary treatment center from GPs and PDs. No major deviations from Danish guidelines were found.

KEYWORDS

atopic dermatitis, general practice, practicing dermatologist, referral pattern

INTRODUCTION

Atopic dermatitis (AD) is a common eczematous inflammatory skin disease that affects 15%–20% of children and 3%–5% of adults in affluent countries.[1–3] The condition usually develops in childhood and resolves before adolescence in 80% of cases.[4] Yet, recent studies have found that persistence into adulthood and adult-onset AD is higher than previously thought.[5,6]

AD often has a unique presentation with localised lesions predominantly on hands, face, or flexural body parts, in an age-dependent manner. In rare cases, patients are erythrodermic with involvement of >90% of the body surface.[1] Despite these characteristic patterns, the clinical presentation and the severity of disease can vary significantly. This heterogenous nature can pose a challenge for general practitioners (GPs) in the diagnosis and treatment of AD.

Sufficient disease control can often be achieved with topical therapies such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI). Systemic antibiotics may be needed in the case of secondary infection.[1,7–11] Systemic corticosteroids are not recommended in Danish nor international guidelines, except for acute severe flares in AD as a short-term solution.[8,12,13]

Severe and treatment-refractory cases require specialised treatment either by practicing dermatologists (PDs) in the primary sector or by hospital-based dermatology departments in the secondary and tertiary sector.[14–16] Dermatologists have extended treatment options incl. phototherapy with artificial ultraviolet radiation and systemic treatment with conventional immunosuppressive drugs such as Methotrexate (MTX), Azathioprine (AZA), Mycophenolate mofetil (MMF) and Cyclosporine A (CsA).[8,17–20]

Newer biological and small molecule immunomodulatory drugs, including monoclonal antibodies targeting the IL4/IL-13 axis and Janus Kinase Inhibitors (JAKi) with a broader but still selected inhibition of cytokines, have emerged in the treatment of AD, offering more efficacious treatment than the conventional drugs.[21–23] In many countries, including Denmark, these drugs may only be prescribed by specialized dermatology departments located at larger university hospitals, which constitutes the tertiary sector in Denmark.[8,14,15]

Patients with AD are primarily handled in the primary care sector in Denmark, with GPs acting as gatekeepers both for referral to PDs in the primary sector and direct referral to hospital-based dermatology departments in the secondary and tertiary sectors. National guidelines for handling patients with AD are in line with international guidelines,[8,12,13] but no specific regional guidelines on collaboration between GPs, PDs and hospital specialist care exits.

The aim of this study was to investigate the treatment and referral patterns of AD from GPs and PDs, to compare these, and to investigate if there are any knowledge gaps in either sector that should be addressed.

METHODS

Study design and setting

This retrospective cohort study was performed on a random sample of patients with AD referred to the Department of Dermatology, Aarhus University Hospital (AUH) in the Central region of Jutland, Denmark from 2019 to 2021. Data regarding referral content, first consultation in the hospital and treatment before and post-hospital referral was obtained from the patients' medical records and typed into a standardised chart in REDCap.[24]

The study was performed according to local guidelines for the collection of information from patient files and according to Danish laws.

Patient selection

A list of patients was extracted through diagnosis and referral codes for AD: L20, L200, and L209 + Z0150. The

search was restricted to patients who had been referred to the Department of Dermatology, AUH and treated in the period between 2019 and 2021, both years included.

The list consisted of 386 patients. To ensure a random sample every fourth patient ($n = 97$) was selected. Upon perusal of their medical records, 16 patients were excluded due to missing referrals in the patients' medical files, treatment initiation before 2019 or another diagnosis than AD. Four patients were lost to follow-up, that is, not eligible for the second analysis regarding treatment.

We decided to further include every 12th patient on the list ($n = 33$). Two cases appeared twice on the list, had already been assessed in the first round, and were therefore excluded from the second round. Further, two cases were lost to follow-up, thus not eligible for a second analysis.

The final cohort consisted of 112 cases eligible for the first analysis regarding referral patterns and 106 cases eligible for the second analysis regarding treatment. The process of exclusion is depicted in Figure 1.

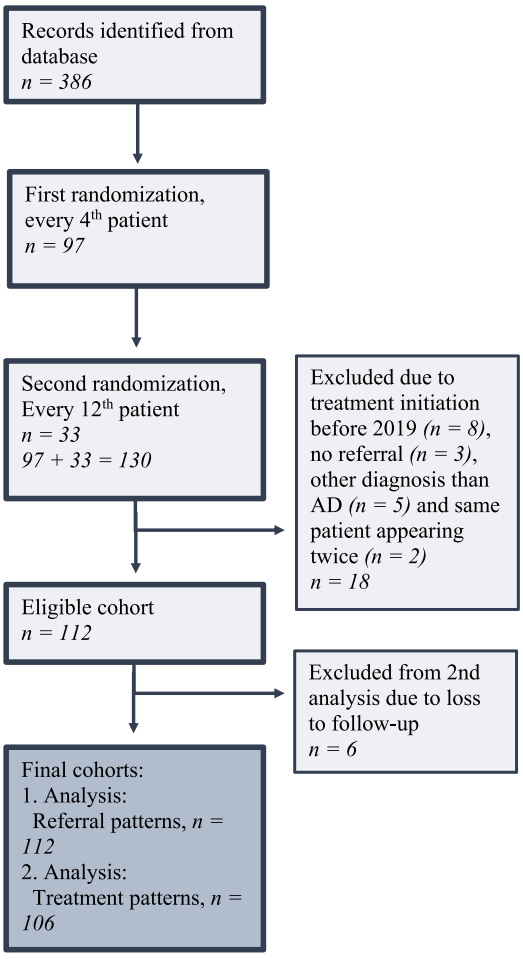

FIGURE 1 Inclusion/exclusion process of patients. Flow diagram over the inclusion process. The final cohort consisted of 112 patients for analysis of referral patterns and 106 patients for analysis of treatment patterns. n, number of observations.

Variables

All information was obtained from the patients' medical records. General information consisted of gender, age at first consultation, date of referral, and date of first consultation.

Concerning referral characteristics, the following information was obtained: type of referring doctor and zip code, reason for referral, descriptive information in the referral (severity of AD, severity of itch, severity of sleep disturbance, allergies, other comorbidities, prior treatment, and reasons for discontinuation).

Concerning the first consultation at the hospital department, the following information was obtained: severity of AD, prior treatment and number of times dispensed at the pharmacy within the 12 months before first consultation. Regarding further treatment at the hospital, the following information was obtained: none/continuation of topical treatment, systemic treatment (MTX, AZA, CsA, Dupilumab, and Baricitinib), the efficacy of the treatment, and if discontinuation; reason for this, and possible initiation of the second or third drug (Updacitinib and Abrocitinib were not available in Denmark until 2023).

Statistical analysis

The statistics were performed in Excel and STATA/SE 17.[25] Qualitative data were analysed with a quantitative approach by respective calculation of actual numbers and percentages. Because of skewed distribution, quantitative data were reported by medians and interquartile ranges (IQR). Due to the relatively small group sizes, differences were investigated with Fisher Exact test. If possible (group size > 5 individuals), a χ^2 test was also performed to ensure precise p-values. Since the p-values obtained through the two statistical tests only varied slightly and did not change the significance outcome, only the p-values obtained through the Fisher Exact test were reported in this article.

RESULTS

Most patients with AD are referred to hospitals from the primary sector

The cohort consisted of 112 eligible cases; 57 (50.9%) females. Baseline characteristics are displayed in Table 1. Age varied from 0 to 84, with a median age at first hospital consultation of 17.5 years (IQR = 28.75). Most of the cohort had been referred from the primary sector by PDs (45.5%)

TABLE 1 Demographic data.

n = 112 **Demographics**	*n* (%)/ **Median (IQR)**	**Range**
Male	55 (49.1)	
Female	57 (50.9)	
Age at first consultation, years	17.5 (28.75)	0–84
Median (IQR)		
Referring doctor		
General practitioner	27 (24.1)	
Private practicing dermatologist	51 (45.5)	
Paediatric hospital department	20 (17.9)	
Other hospital department	9 (8)	
Other	5 (4.5)	
Status of treatment course at hospital		
Ended	43 (38.4)	
Still active	69 (61.6)	
Duration of treatment at hospital, days*	210 (309)	0–572
Median (IQR)		

Abbreviations: IQR, interquartile range; *n*, number of observations.
*Analysis was conducted on the subgroup of ended observations only (*n* = 43).

and GPs (24.1%). From the secondary sector, most of the patients were referred by paediatric hospital departments (17.9%) and other hospital departments (8%). Finally, a small group of patients was referred by other physicians in the primary sector (4.5%), for example, private paediatricians, pulmonologists, allergologists, and so forth.

The median duration of treatment and follow-up in the hospital setting was 210 days (IQR = 309), and 38.4% of the cohort had ended their treatment at the hospital when the present study was performed. The remaining 61.6% were still undergoing treatment and attending regular consultations at the hospital.

GPs refer to hospital on acute indication while PDs refer on lack of disease control

We found a significant difference between GPs and PDs in their stated indications for referral (Table 2). Acute flare-ups, that is, acute rash, secondary infections, intolerable itching, pain, or social consequences, were the main reasons for referral from the GPs (40.7%). By contrast, only 3.9% of the patients referred from PDs were due to acute need of treatment (p-value = 0.0001). The primary reason for referral from PDs was insufficient disease control (64.7%), that is, flare-up immediately after cessation of topical therapy, non-responders to topical therapy, or non-responders to all available therapies, which was only the case in 25.9% of the patients referred from GPs (p-value = 0.0018).

In total, 92.9% of the doctors described previous treatment(s) in their referral statement, with no statistical difference between GPs and PDs (p-value = 1.000).

TCS were the preferred drugs, and 94.2% of the patients, for whom previous treatment was described, had received TCS before referral. Systemic steroids were not widely used, but highest among PDs (18.8%). The use of other systemic immunosuppressive therapies was reported almost exclusively by the PDs, which is to be expected, as these drugs are reserved for dermatologists only. Patients for whom treatment with systemic immunosuppressive drugs were reported by other doctors e.g., GPs indicated that the patients had previously been treated by a dermatologist. Use of TCIs were primarily reported by PDs (41.7%) compared with GPs (16%).

The main reason for discontinuation of all treatments was insufficient response (55.8%) but many of the patients (28.8%) had not discontinued treatment at time of referral. Adverse events and compliance issues as reason for discontinuation were less common.

Additional highly relevant and valuable information in the referral is itch symptoms, sleep disturbances, allergies and other comorbidities. Itch was mentioned in 48.2% of GP-referred cases and sleep disturbance in 33.3%, compared to PD-referred cases where itch and sleep disturbance was mentioned in 31.4% and 9.8% of cases, respectively. However, only the difference observed for describing sleep disturbance was significant (p-value = 0.0144).

For allergies and other comorbidities, the percentages were nearly similar between the two groups. GPs reported other comorbidities more often than PDs (33.3% vs. 27.5%), whereas PDs reported allergies more often than GPs (39.2% vs. 25.9%). These differences were not statistically significant.

Assessed severity differs from primary to tertiary sector

AD was described as severe in 57.1% of all cases in the referral (Table 3). By contrast, only 28.6% of all cases were described as severe at first hospital consultation. A comparison of the severity descriptions between the referring doctor and the hospital dermatologist was

TABLE 2 Information regarding indication for referral, prior treatment, and descriptive factors from referrals.

n = 112	GP	PD	Paediatric hospital dep.	Other hospital dep.	Other	Total	*p*-Value*
Indication of referral							
Acute (itching, rash, infection, pain, and social consequences)	11 (40.7)	2 (3.9)	3 (15)	1 (11.1)	-	17 (15.2)	0.0001
Lacking disease control	7 (25.9)	33 (64.7)	12 (60)	1 (11.1)	2 (40)	55 (49.1)	0.0018
Need for systemic treatment	2 (7.4)	8 (15.7)	1 (5)	1 (11.1)	1 (20)	13 (11.6)	0.4797
Reluctance to treatment from parents	1 (3.7)	-	-	-	-	1 (0.9)	0.3462
Low compliance to treatment	-	2 (3.9)	-	-	-	2 (1.8)	0.5415
Other/not specified	6 (22.2)	6 (11.8)	4 (20)	6 (66.7)	2 (40)	24 (21.4)	0.3226
Was prior treatment reported							
Yes	25 (92.6)	48 (94.1)	18 (90)	8 (88.9)	5 (100)	104 (92.9)	1.000
No	2 (7.4)	3 (5.9)	2 (10)	1 (11.1)	-	8 (7.1)	
Which treatments							
TCS	24 (96)	45 (93.8)	18 (100)	7 (87.5)	4 (80)	98 (94.2)	1.000
Systemic steroids	2 (8)	9 (18.8)	-	-	2 (40)	13 (12.5)	0.3111
MTX	2 (8)	12 (25)	-	1 (12.5)	-	15 (14.4)	0.1182
AZA	1 (4)	11 (22.9)	-	1 (12.5)	-	13 (12.5)	0.0481
CsA	-	-	-	2 (25)	-	2 (1.9)	1.000
Antihistamines	3 (12)	4 (8.3)	1 (5.6)	1 (12.5)	-	9 (8.7)	0.6847
TCI	4 (16)	20 (41.7)	6 (33.3)	2 (25)	2 (40)	34 (32.7)	0.0359
Other	7 (28)	16 (33.3)	3 (16.7)	3 (37.5)	2 (40)	31 (29.8)	0.7920
Reasons for discontinuation of all treatments							
Insufficient effect	11 (44)	28 (58.3)	12 (66.7)	5 (62.5)	2 (40)	58 (55.8)	0.3239
Adverse event	1 (4)	6 (12.5)	2 (11.1)	-	-	9 (8.7)	0.4101
Low compliance	2 (8)	2 (4.2)	-	1 (12.5)	1 (20)	6 (5.8)	0.6027
Not discontinued	11 (44)	13 (27.1)	4 (22.2)	1 (12.5)	1 (20)	30 (28.8)	0.1909
Other	-	1 (2.1)	1 (5.6)	-	1 (20)	3 (2.9)	1.000
Not described	-	3 (6.3)	1 (5.6)	1 (12.5)	-	5 (4.8)	0.5466
Descriptive factors							
Reported moderate-severe itch symptoms	13 (48.2)	16 (31.4)	6 (30)	2 (22.2)	2 (40)	39 (34.8)	0.2178
Reported moderate-severe sleep disturbance	9 (33.3)	5 (9.8)	4 (20)	1 (11.1)	-	19 (16.9)	0.0144
Reported other comorbidities	9 (33.3)	14 (27.5)	9 (45)	5 (55.6)	3 (60)	40 (35.7)	0.6102
Reported allergies	7 (25.9)	20 (39.2)	9 (45)	2 (22.2)	3 (60)	41 (36.6)	0.3191

Note: Reported numbers are *n* (%).

Abbreviations: AZA, azathioprine; CsA, cyclosporine A; dep, department; GP, general practitioner; MTX, methotrexate; n, number of observations; PD, practicing dermatologist; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

*All Fisher's exact tests were performed only on GPs versus PDs. A p-value < 0.05 was considered significant.

**Note that the numbers exceed the sum in some of the variables, because the cases often had outcomes in more than one subgroup or variable, e.g., received more than one treatment, had more than one reason for discontinuation, had both comorbidities and allergies, etc.

TABLE 3 Description of severity of atopic dermatitis in the referral and at the hospital.

n = 112	GP	PD	Paediatric hospital dep.	Other hospital dep.	Other	Total	*p*-Value*
Severity described in referral							
Mild	2 (7.4)	-	-	1 (11.1)	-	3 (2.7)	0.1169
Moderate	1 (3.7)	5 (9.8)	1 (5)	1 (11.1)	-	8 (7.1)	0.6585
Severe	18 (66.7)	32 (62.7)	9 (45)	3 (33.3)	2 (40)	64 (57.1)	0.8073
Not described	6 (22.2)	14 (27.5)	10 (50)	4 (44.4)	3 (60)	37 (33)	0.7864
Severity described at first hospital consult							
Mild	8 (29.6)	13 (25.5)	12 (60)	3 (33.3)	2 (40)	38 (33.9)	0.7901
Moderate	6 (22.2)	12 (23.5)	-	2 (22.2)	-	20 (17.9)	1.000
Severe	7 (25.9)	16 (31.4)	5 (25)	3 (33.3)	1 (20)	32 (28.6)	0.7948
Not described	6 (22.2)	10 (19.6)	3 (15)	1 (11.1)	2 (40)	22 (19.6)	0.7764
Comparison							
Less severe	9 (33.3)	12 (23.5)	7 (35)	1 (11.1)	1 (20)	30 (26.8)	0.4242
As severe	9 (33.3)	18 (35.3)	3 (15)	4 (44.4)	1 (20)	35 (31.3)	1.000
More severe	-	-	-	-	-	-	1.000
Not described	9 (33.3)	21 (41.2)	10 (50)	4 (44.4)	3 (60)	47 (42)	0.6261

Note: Reported numbers are *n* (%).

Abbreviations: dep, department; GP, general practitioner; n, number of observations; PD, practicing dermatologist.

*All Fisher's exact tests were performed only on GPs versus PDs. A *p*-value < 0.05 was considered significant.

conducted on each case. For 31.3% of patients the severity at first hospital consultation agreed with the severity described at referral. For 26.8% it was less severe, and in no cases more severe. For 42% either the referring doctor or the hospital dermatologists had not provided a description of the severity in the referral or patient file, respectively.

Slightly fewer of the patients referred from a PD were less severe than described at referral (23.5%) compared to those from GPs (33.3%). However, there was no statistical difference.

Moderate-potent topical corticosteroids are the most used drugs before referral

We compared the information given in the referral, the information given by the patient at first consultation, the patients' electronic medical files (*Elektroniske Patient Journal* [EPJ]), and the electronic database of prescriptions (*Fælles Medicinkort* [FMK]), which also included information on how much of a given prescription the patients had actually collected at the pharmacy (Table 4).

The most frequently used drug was moderate-potent TCS (II–III) (87.5% and 72.3%). Mild-moderate TCS (I–II) was more frequent among the paediatric referrals (65% and 95%). All potencies of TCS were prescribed equally by GPs and PDs. Conversely, systemic steroids as well as systemic immunosuppressants were used more among the patients referred from PDs compared with GPs.

TCIs were widely used among the patients from PDs (64.7%) and less frequent in the patients referred from GPs (25.9%), with a statistically significant difference (*p*-value = 0.0018).

Methotrexate is the most used systemic treatment after referral

In these analyses, the cohort consisted of 106 patients (Table 5). Six patients from the original cohort ($n = 112$) were excluded from this part of the study due to insufficient registration of information regarding their treatment.

A large part of the patients (57.6%) continued receiving only topical therapy for their AD after referral; 50% of GP patients, 46% of PD patients and 95% of paediatric department hospital patients.

Patients were offered systemic treatment in 50% of the cases among GP patients and 44% of the PD patients.

TABLE 4 Treatment for atopic dermatitis ahead of referral, categorised by referring doctor/department.

n = 112	GP	PD	Paediatric hospital dep.	Other hospital dep.	Other	Total	*p*-Value*
Treatments							
TCS gr 1 (hydrocortisone)	9 (33.3)	15 (29.4)	13 (65)	2 (22.2)	2 (40)	41 (36.6)	0.7985
TCS gr 2 (hydrocortisone-17-butyrate)	23 (85.2)	44 (86.3)	19 (95)	8 (88.9)	4 (80)	98 (87.5)	1.000
TCS gr 3 (mometason furoate)	21 (77.8)	41 (80.4)	9 (45)	7 (77.8)	3 (60)	81 (72.3)	0.7764
TCS gr 4 (clobetasol propionate)	9 (33.3)	15 (29.4)	3 (15)	2 (22.2)	2 (40)	31 (27.7)	0.7985
TCS w. antibiotics (fucidic acid, clioquinol etc.)	8 (29.6)	15 (29.4)	-	2 (22.2)	2 (40)	27 (24.1)	1.000
Systemic corticosteroids	3 (11.1)	15 (29.4)	-	1 (11.1)	2 (40)	21 (18.8)	0.0918
MTX	2 (7.4)	12 (23.5)	-	1 (11.1)	-	15 (13.4)	0.1204
AZA	2 (7.4)	11 (21.6)	-	1 (11.1)	-	14 (12.5)	0.1998
CsA	-	-	-	2 (22.2)	-	2 (1.8)	1.000
TCI	7 (25.9)	33 (64.7)	8 (40)	5 (55.6)	3 (60)	56 (50)	0.0018
Other**	8 (29.6)	12 (23.5)	3 (15)	2 (22.2)	2 (40)	27 (24.1)	0.5932
None	1 (3.7)	-	-	-	-	1 (0.9)	0.3462

Note: Reported numbers are *n* (%).

Abbreviations: AZA, azathioprine; CsA, cyclosporine A; dep, department; GP, general practitioner; MTX, methotrexate; *n*, number of observations; PD, practicing dermatologist; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

*All Fisher's exact tests were performed only on GPs versus PDs. A p-value < 0.05 was considered significant.

**Other treatments included UV therapy, red baths with potassium-permanganate solutions, etc.

Ten per cent of the PD patients were already on systemic therapy and were kept on that but increased in dosage.

One patient (5%) referred from a paediatric hospital department received systemic treatment.

No statistical significance in difference of the percentage of patients treated with systemics upon referral was found between GPs and PDs. The difference was significant for the paediatrics compared to both GPs and PDs (p-values = 0.0020 and 0.0001).

Sixty per cent of all referred patients received MTX as their first-line drug, and 20% received AZA, making these the preferred drugs in first-line systemic treatment of AD. MTX was effective in 37% of cases, AZA in 44.4%. For second-line treatment, CsA and Dupilumab were the preferred drugs, of which 66.7% and 100% respectively achieved sufficient effect. Due to small sample sizes, data were not robust regarding Baricitinib ($n = 1$, first-line), and third-line treatment ($n = 3$, Dupilumab).

DISCUSSION

This study investigated the health characteristics of patients with AD and provided information on the current cooperation across Danish healthcare sectors. Particularly information on patients referred from the GPs and PDs who represent most of the patients referred to the Department of Dermatology, Aarhus University Hospital (AUH). An interesting finding was the difference in *indication of referral* between GPs and PDs.

GPs primarily referred due to acute need of treatment, while PDs mostly referred due to lack of disease control. Apart from the apparent differences in specialisation and experience with skin conditions, this difference could be explained by the discrepancy in treatment options. GPs can only offer topical therapies and systemic corticosteroids, and considering that the latter is generally not recommended, their options are quickly exhausted. PDs have extended privileges with conventional systemic drugs and UV therapy, thus allowing better opportunities for the treatment of acute AD flares. Second, this may indicate a tendency to refer acute flares directly to specialized departments, while those who can wait, possibly more chronically affected patients, are referred to a PD. The latter group often being the treatment-refractory patients, thereby contributing to the PDs main indication of referral; lack of disease control. Regional guidelines for GPs describing the best pathways for referral in collaboration with PDs and secondary/tertiary specialist care would probably strengthen the collaboration and benefit patients with severe AD regarding efficient referral and start of treatment.

TABLE 5 Selected/initiated therapy for atopic dermatitis at Department of Dermatology, Aarhus University Hospital.

n = 106	GP	PD	Paediatric hospital dep.	Other hospital dep.	Other	Total	*p*-Value*
None/continuation of topical treatment	12 (50)	23 (46)	19 (95)	3 (42.9)	4 (80)	61 (57.6)	GP vs. PD:0.8067 GP vs. Ped:0.0020 PD vs. Ped:0.0001
Initiation of systemic treatment	12 (50)	22 (44)	1 (5)	4 (57.1)	1 (20)	40 (37.7)	GP vs. PD:0.8036 GP vs. Ped:0.0020 PD vs. Ped:0.0016
Dose increase of existing systemic treatment	-	5 (10)	-	-	-	5 (4.7)	GP vs. PD:0.1671 GP vs. Ped:1.000 PD vs. Ped:0.3117
Total	24 (22.6)	50 (47.2)	20 (18.9)	7 (6.6)	5 (4.7)	106	

Type of systemic treatment	**MTX**	**AZA**	**CsA**	**Dupilumab**	**Baricitinib**
First line *n = 45*	27 (60)	9 (20)	3 (6.7)	5 (11)	1 (2.2)
Effect**					
Yes	10 (37)	4 (44.4)	1 (33.3)	2 40)	1 (100)
No	17 (63)	5 (55.6)	2 (66.7)	3 (60)	
Second line *n = 20*	2 (10)	2 (10)	6 (30)	10 (50)	-
Effect**					-
Yes	-	-	4 (66.7)	10 (100)	-
No	2 (100)	2 (100)	2 (33.3)	-	-
Third line *n = 3*	-	-	-	3 (100)	-
Effect**					
Yes	-	-	-	3 (100)	-
No	-	-	-	-	-

Note: Reported numbers are *n* (%).

Abbreviations: dep, department; GP, general practitioner; *n*, number of observations; PD, practicing dermatologist; ped, paediatric.

*Fisher's exact tests were performed on GPs versus PDs, GPs versus Paediatric hospital dep. and PDs versus Paediatric hospital dep. A p-value < 0.05 was considered significant.

**Effect was defined as subjective and objective disease control within 6 months of compliant use.

GPs were better at including descriptive information (itch, sleep and comorbidities) in their referrals than PDs, yet only the difference in description of sleep disturbance was significant. This may be explained by the fact that GPs manage a heterogenous patient group demanding a broad approach when obtaining anamnestic information. PDs might consider pruritus and consequential sleep disturbance as a matter of course and are therefore less inclined to mention it.

Furthermore, a referral from a GP straight to a tertiary department may be at higher risk of getting rejected compared to those from PDs, thus forcing GPs to write more thorough referrals. Patients with less severe disease or less pronounced symptoms may also be referred from the GPs to the PDs, thereby leaving only the very special cases to be referred to the tertiary center, skewing the results of this investigation. All though GPs to a higher degree than PDs include information on itch, sleep, and comorbidities it was only the case in half of the referrals and better guidelines for information in referrals should be developed.

TCS was the preferred drug across all referring doctors, corresponding well with the national guidelines for AD. Yet, the efficacy of TCS is highly reliant on correct use. A limitation to this study was the lacking information regarding the provided instructions, patient

compliance etc. While we can conclude that TCS is widely used, we are unable to further quantify this result or to tell whether the efficacy differs depending on the prescribing doctor.

No significant differences were found in the treatment patterns, except for TCI. Significantly fewer of the patients referred from a GP had received TCI compared to those referred from a PD (p-value = 0.0018). Considering that this is a topical option also available for GPs to prescribe, we would have expected a higher prevalence. It is possible that many GPs are unaware of or have too little experience with this treatment option. Some GPs may also be afraid of using these products due to the black box warning. This demonstrates the relevance of a guideline for GPs, as well as continuous medical education.

While observations in this present study generally aligns with the national treatment guidelines, previous Danish studies have found discrepancies, suggesting both overuse of systemic corticosteroids and antibiotics as well as undertreatment with both potent to very potent TCS (III–IV) and conventional systemic therapies.[26,27] In these studies, it is uncertain whether the low use of potent to very potent TCS is a sign of undertreatment by the doctors or a sign of undereducation and possibly corticophobia among the patients, the latter being a well-known issue in dermatology patients.[28] The conventional systemic therapies were generally more represented amongst PD-referred patients (MTX: 23.5%; AZA: 21.6%). This was to be expected, as these can only be prescribed by dermatologists, and not GPs. Yet, considering that the PDs' main indication of referral was lacking disease control and 62.7% of the PD-referred cases were described as severe in the referral, one could argue that there is a stark contrast between the burden of disease and the number of established treatments being prescribed in this study.

Approximately half of the patients referred from GPs and PDs were offered systemic treatment at the hospital. Most of the patients received MTX (60%) followed by AZA (20%) as first-line treatment.

No statistical significance in difference was found between GP and PD referred patients but a significant difference was found between paediatric-referred patients and GPs and PDs, respectively. However, only one paediatric-referred patient received systemic treatment after referral. Furthermore, comparing age-varying groups (GPs and PDs) with age-restricted groups (paediatric hosp. dep.) is not ideal. While MTX and AZA has been found safe and equally effective in children,[29] other guidelines apply for paediatric patients compared to adults, and systemic treatment for children is reserved for very severe cases where the negative consequences of the disease outweigh the possible adverse effects of the medication.[12,13]

A final limitation to this study is the study population. The study was constructed in a manner, that only included accepted referrals. Due to the study design, it was not possible to retrospectively include the rejected referrals that did not meet criteria to be accepted in a tertiary center. This poses a substantial risk of selection bias and may have skewed the results in a more "positive" direction. A prospective follow-up study is needed to include the rejected referrals and further comment on potential challenges in the referral patterns.

CONCLUSION

This study provides an overview of the current treatment and referral patterns in a cohort of Danish AD patients. The results indicate that GPs and PDs manage AD in the primary care sector mostly according to national and international guidelines. There are possible gaps in the use of TCIs among GPs and a lack of use of systemics among PDs. Though, these results may be positively skewed due to selection bias. The results sheds light on differences between GPs, PDs and hospital-based paediatricians that may aid in the daily clinical work as well as in the formation of a guideline, if further research deems it necessary.

AUTHOR CONTRIBUTIONS

Anna Kathrine Danielsen: Has conducted the data extraction, management, and statistical analyses. Anna Kathrine Danielsen has also written the draft of the article. Anne Sofie Frølunde: Has designed the study together with Christian Vestergaard and been responsible for approvals, preparation of the study, supervising Anna Kathrine Danielsen during data extraction and management, and critically revising the manuscript. Sofine Heilskov: Attributed to data collection and critically reviewed the manuscript. Mette Deleuran: Has critically reviewed the manuscript. Janus Laust Thomsen: Has critically reviewed the manuscript. Christian Vestergaard: Has designed the study together with Anne Sofie Frølunde, supervised Anna Kathrine Danielsen and Anne Sofie Frølunde and critically reviewed the manuscript.

CONFLICT OF INTEREST STATEMENT

AKD, ASF, SH, and JLT have no conflicts of interest. MD has received honoraria from AbbVie, Pierre Fabre,

La Roche Posay, Leo Pharma, Lilly, Incyte, Sanofi Genzyme, Regeneron, Pfizer, Kymab, and Almirall. CV has received honoraria from Abbvie, Sanofi, Almiral, Novartis, LEO Pharma, Astra Zeneca, Pfizer, Galderma and is the President of the Nordic dermatology association.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

ETHICS STATEMENT

The study has been approved by the heads of the Department of Dermatology, Aarhus University Hospital.

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