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Original Article

The treatment journey of children with moderate to severe atopic dermatitis in Türkiye: unmet needs

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ABSTRACT

Background. Atopic dermatitis (AD) substantially burdens individuals, families, and healthcare systems. We aimed to document the treatment journey of pediatric patients with moderate-to-severe AD in a referral center based in our country.

Methods. This retrospective study reviewed patients aged 1-18 years diagnosed with AD, seeking systemic treatment recommendations from the "pediatric allergy and dermatology multidisciplinary team meeting".

Results. Over the 14-month study period, 30 (12.5%) of 240 AD patients were evaluated in the pediatric dermato-allergy team meetings. The median age of the patients was 13.66 years (Q1-Q3: 7.94-17.27), of whom 60% were male. The median annual healthcare visits for AD were 4 (Q1-Q3: 1.00-8.75). Among the study group, 70% were sensitized to aeroallergens, and admission markers included total IgE (median: 1980 IU/mL, Q1-Q3: 794.50-5446), and eosinophil counts (median: 650, Q1-Q3: 275-1275). All patients utilized intermittent and/or continuous topical corticosteroids (CS), with 56.6% employing short-term/long-term topical tacrolimus. Over the past two years, systemic CSs were utilized in 93.3% of the patients, whereas 57.1% received more than one course. Approximately 43.3% of the patients agreed to receive systemic cyclosporine treatment, with only 30.8% benefiting and 3.3% reporting adverse effects (hypertrichosis and cellulitis). Three patients self-funded dupilumab, all benefiting without adverse effects. Omalizumab, mycophenolate mofetil and narrow-band ultraviolet (UV) treatments were used in one patient each, with limited benefit observed. Health insurance did not grant approval for a Janus kinase inhibitor for one patient.

Conclusions. Managing moderate to severe AD is complex and costly, considering disease heterogeneity, comorbidities, care pathways, and health system challenges. Addressing the unmet needs should be a priority in Türkiye's healthcare systems.

Key words: adolescent, atopic dermatitis, children, healthcare, systemic, treatment.

Atopic dermatitis (AD) is a chronic inflammatory skin disease that can cause a great deal of discomfort and distress for patients, their families, and the healthcare system.[1,2] It is particularly challenging to manage the moderate-to-severe spectrum, where patients often require systemic medications to control their symptoms.[3,4]

Managing AD involves proper skin care and trigger avoidance, with primary treatment using corticosteroids (CS) and calcineurin inhibitors during flare-ups, proven effective and safe in the short term.[5] In resistant or recurrent cases, a proactive approach may be considered. Severe AD is characterized by extensive body surface involvement, resistant lesions, and permanent skin changes.[6] Another definition is treatment necessity, considering it is unresponsive to

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topical treatments.[7] For severe AD, systemic immunosuppressants, narrow-band ultraviolet B (UVB), biologic therapies like dupilumab, or Janus kinase (JAK) inhibitors may be necessary. However, these pose greater responsibility, with increased risks and costs compared to first-line treatments. Caution is crucial, especially when prescribing to pediatric patients. Systemic steroids, effective in controlling severe flare-ups, are only used for short courses due to their potential adverse effects.

Türkiye is home to a diverse population with a wide range of healthcare needs. However, there is a lack of data on the treatment journey of pediatric patients with moderate-to-severe AD in this region. Therefore, the results of this study will be valuable for clinicians, policymakers, and other stakeholders who are working to improve the care of pediatric patients with moderate-to-severe AD in this region. This study aims to fill this gap by providing insights into the treatment patterns and outcomes of these patients.

Methods

This retrospective study was conducted in a tertiary care center in Türkiye to document the clinical characteristics and treatment journeys of pediatric patients with moderate-to-severe AD. The study cohort included children and adolescents aged 1-18 years who were assessed for AD during pediatric allergy-dermatology team meetings between August 1, 2021, and October 1, 2022. These patients were referred due to inadequate control of their AD with topical treatments, prompting the need for evaluation for systemic treatment options. Pediatric allergy-dermatology multidisciplinary team meetings focused on the evaluation and management of children and adolescents (aged 1-18 years) with AD refractory to topical treatment or experiencing frequent relapses, indicating a potential need for systemic therapy. These complex cases were presented to a multidisciplinary team of consultants, fostering collaborative discussion and shared decision-making.

Patient data collection

The patient information that was analyzed included their age, gender, age at the initial diagnosis of AD, details of topical and systemic treatments administered for eczema, concurrent comorbidities, levels of specific and total immunoglobulin E (IgE), blood eosinophil counts, healthcare visit frequency, coexisting respiratory and food allergies, as well as any alternative or complementary drug therapies employed. This information was gathered through both face-to-face interviews with patients and their parents and electronic medical records. Clinical data reported by patients and parents were cross-referenced with the records maintained by emergency and allergy units within the healthcare system.

Diagnosis of the atopic disease

The patients were diagnosed with AD according to the Hanifin and Rajka criteria. The inclusion criteria for the study were moderate-severe AD, inadequate control with topical treatments and involvement of at least 25% of the body surface area. Objective SCORAD scores of the patients were recorded to evaluate the degree of atopic eczema. Diagnoses of allergic rhinitis and asthma were made by following international guidelines.[8-10]

Skin prick tests, serum total, and specific IgE measurements

Skin prick tests (SPTs) were administered according to the patient's clinical history, including respiratory allergies and suspected food allergies. Common aeroallergens and cross-reactive food allergens were tested, as previously described.[2,11] SPTs were conducted using histamine (10 mg/mL) and saline controls. Wheal size was measured after 15 minutes. The diagnosis of food allergy depended on demonstrating IgE sensitization through an SPT (≥ 3 mm) and/or a positive specific IgE (sIgE) level (≥ 0.30), in conjunction with a positive oral food challenge (OFC) or a consistent history of IgE-mediated allergy. In the absence of an OFC and consistent history, any SPT and/

or sIgE levels that exceeded the 95% positive predicted value (PPV) for clinical reactivity were considered. If the 95% positive PPV was not explicitly specified for any food, the criteria applied were sIgE ≥ 15 kU/L and/or SPT ≥ 8 mm. Resolved food allergy indicates tolerance to a previously allergenic food.[12] Total IgE levels were quantified in serum using the ImmunoCAP method (Thermo Fisher Scientific, Waltham, MA).

Healthcare use

Healthcare utilization was classified as "current" for the preceding year and "lifetime" for a lifetime and was documented in terms of hospitalization, emergency admissions, and scheduled or unscheduled healthcare visits for AD.

Ethical approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol received ethical approval from the Institutional Review Board of Hacettepe University (Approval Number: GO 21/871).

Statistical analysis

Statistical analyses were performed using SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Variables such as age, total IgE, and absolute eosinophil count exhibited non-normal distributions; therefore, the results were presented as medians and interquartile ranges (Q1-Q3).

Prevalence rates for all variables, including specific allergens, asthma, and allergic rhinitis (AR), were calculated based on age, gender, predominant initial symptoms, and family history of atopy. Frequencies and percentages were used to summarize these prevalence rates. A significance level of $P < 0.05$ was adopted for all statistical analyses.

Results

Characteristics of the study group

Over 14 months, 240 patients were referred to the study center for AD. Of these, 30 patients (12.5%) were presented and discussed at the dermatology-allergy team meetings, all of whom were subsequently included in this study.

The median age of the study cohort was 13.66 years, with a range of 7.94 to 17.27 years (p=0.52). Of these, 60% (n=18) were male. The mean follow-up duration at the study center for the entire group was 1.6 years (±0.9). At admission, medians for total IgE, eosinophil count, and eosinophil percentage were 1980 IU/mL (794.50-5446), 650 (275-1275), and 6.75% (3.80-13.15), respectively (p=0.43) (Table I).

Allergic comorbidities

A significant proportion of the study group, comprising 70% (n=21), exhibited sensitization to aeroallergens (Fig. 1). The predominant culprits were grass pollen, affecting half of the participants (50%, n=15), followed by tree pollens, which impacted 26.6% (n=8). Additionally, cat elicited allergies in 30% (n=9) of individuals, while house dust mites were responsible for sensitizations in 16.6% (n=5) of cases. Sensitization to Malassezia was observed in 16.6% (n=5) of participants. Four out of our 12 patients with AR reported experiencing additional exacerbations in their atopic eczema that persisted during the pollen season.

Approximately 40% (n=12) of the study cohort had received previous diagnoses of food allergies. Among those with food allergies, the most commonly implicated allergens were tree nuts (n=6), egg white (n=5), and cow's milk (n=3). Notably, three patients exhibited allergies to multiple food items. The current food allergies were present in 5 patients, including one with shellfish allergy and four with sensitivities to multiple (≥2) tree nuts.

Table I. Demographic and clinical features of patients.

	Preschool children (1-5 years)	School children (6-12 years)	Adolescents (13-18 years)	Entire group (1-18 years)
Total number of patients	6 (20%)	9 (30%)	15 (50%)	30 (100%)
Age, yr	2.6 (1.8-3.6)	8.5 (5.32-11.6)	16.0 (12.6-18.7)	13.66 (7.94-17.27)
Male gender	4 (66.6%)	4 (44.4%)	10 (66.6%)	18 (60%)
Age at initial symptoms, yr	2.44 (0.8-4.0)	6.9 (5.1-9.4)	14.0 (12.2-15.4)	8.8 (4.2-14.0)
Skin dryness, %	50 (15.5-80)	42.5 (25.5-65.5)	50 (27.5-70)	50 (25-70)
Family history of atopic dermatitis	0 (0%)	6 (66.6%)	4 (26.6%)	10 (33.3%)
Total IgE, IU/mL	762 (360-4133)	2529 (1303.50-3891)	1980 (851-6273)	1980 (794-5446)
Blood eosinophils, %	8.70 (3.37-20.85)	11.80 (8.0-14.05)	5.00 (2.60-10.90)	6.75 (3.8-13.1)
Aeroallergen sensitivity	2 (33.3%)	9 (100%)	10 (66.6%)	21 (70%)
Malassezia sensitivity	0 (0%)	2 (22.2%)	3 (20%)	5 (16.6%)
Ever asthma	0 (0%)	1 (11.1%)	4 (26.6%)	5 (16.6%)
Current asthma	0 (0%)	0 (0%)	4 (26.6%)	4 (13.3%)
Ever food allergy	2 (33.3%)	6 (66.6%)	4 (26.6%)	12 (40%)
Current food allergy	1 (16.6%)	2 (22.2%)	2 (13.3%)	5 (16.6%)
Current allergic rhinitis	0 (0%)	6 (66.6%)	6 (40%)	12 (40%)

Categorical data presented as n (%), numerical data as median (interquartile range: Q1-Q3).

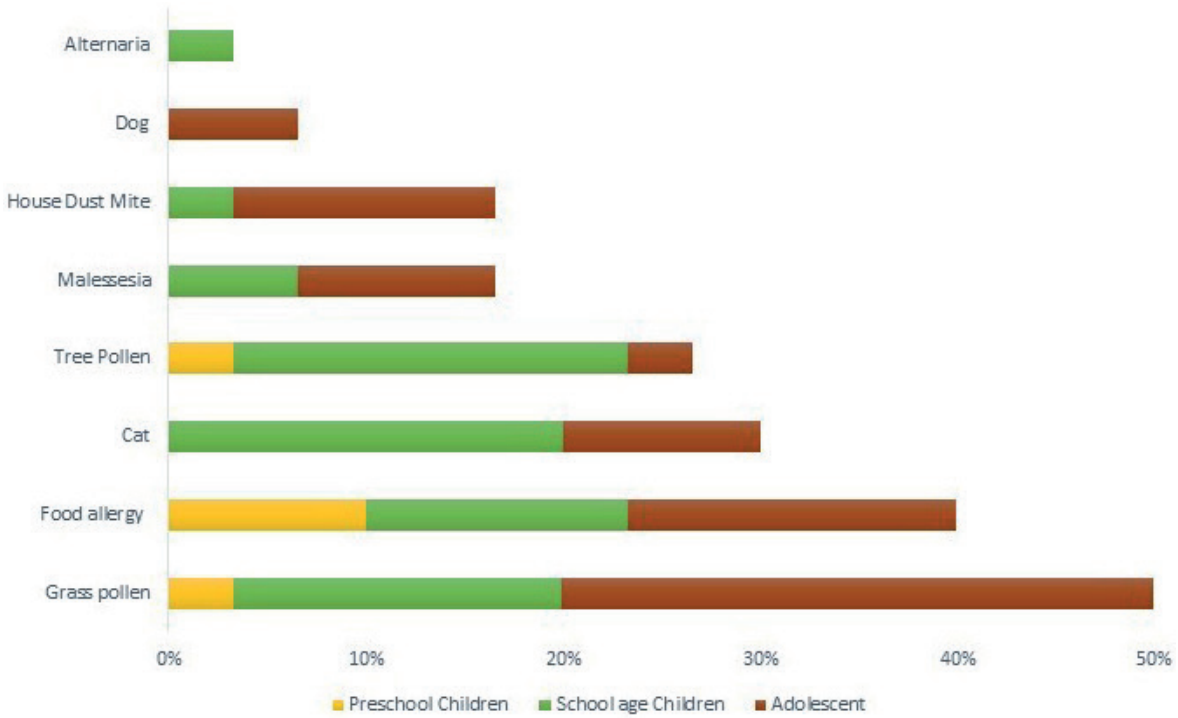

Fig. 1. Allergy frequencies in the study group.

Healthcare resource use (Fig. 2)

The median number of scheduled healthcare visits for AD during the follow-up period was 12 (Q1-Q3: 8.2-17.2). Five patients were admitted to the emergency department, four due to AD exacerbations and one due to cellulitis developed during cyclosporine therapy. Over the past 2 years, median annual healthcare visits for AD were 4 (IQR 1.00-8.75). A total of 5 patients in the study group required hospitalization due to infected AD and received parenteral antibiotic treatment during their stay.

Treatment journey (Fig. 3)

All patients used topical corticosteroids (TCS) and moisturizer intermittently or regularly. Mild-to-moderate strength TCS was used for the face and medium strength TCS was used for the body and extremities. Moderate-strength agents were more preferred as the patient's age increased.

While wet dressing treatment was recommended to half of the patients, it was accepted/tolerated by only 50%. The main concern of those who refused was the fear that the child would catch a cold due to the wet dressing. Although it worked well in almost all patients with repeated application at various intervals, subsequent applications caused adverse effects such as folliculitis. Concerns about potential systemic corticosteroid (SCS) effects, as expressed by physicians who supervised repeated administrations, also led to the discontinuation of treatment.

Our analysis unveiled a substantial dependence on SCS for managing severe AD in the past two years. Notably, 93.3% of patients necessitated a course of SCS lasting more than three days, and 57.1% used SCS on multiple occasions. The median number of SCS occasions in the group was 2.0 (2.0-4.0) per year. Despite an initial improvement observed in all SCS-receiving patients, a concerning 90% experienced relapse within a week of discontinuation. Additionally, six patients required multiple intramuscular depot CS injections, providing an average relief period of three weeks. Although all of these patients benefited from the SCS treatments, recurrence developed within one week after stopping the treatment in 90%. Additionally, 6

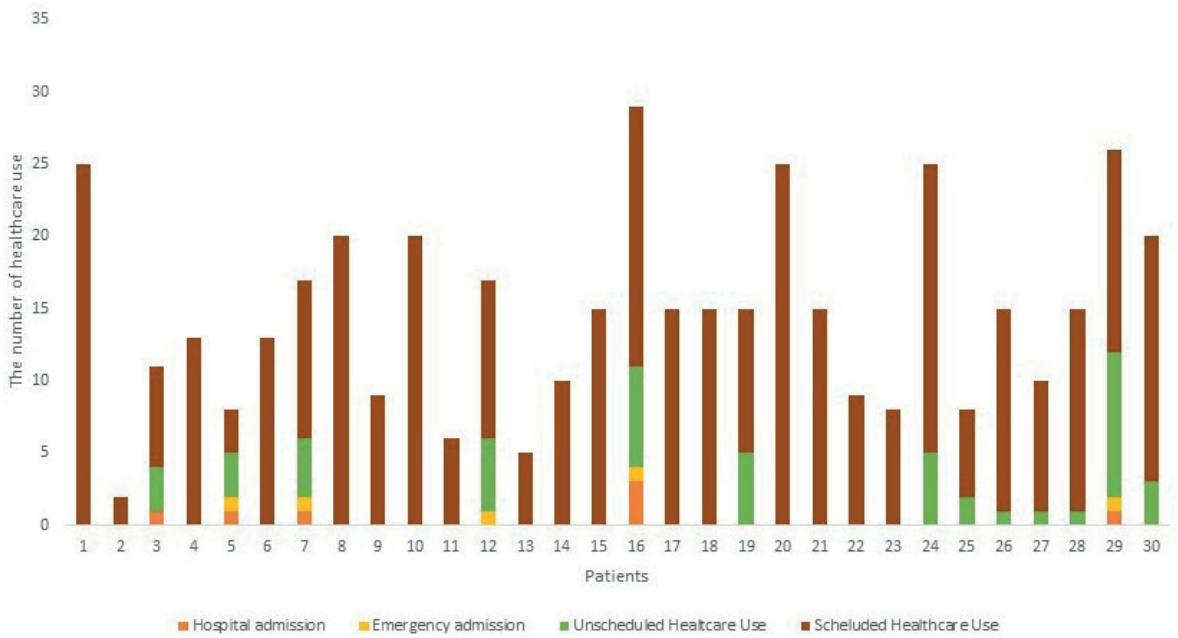

Fig. 2. Lifetime healthcare use for atopic dermatitis of each individual.

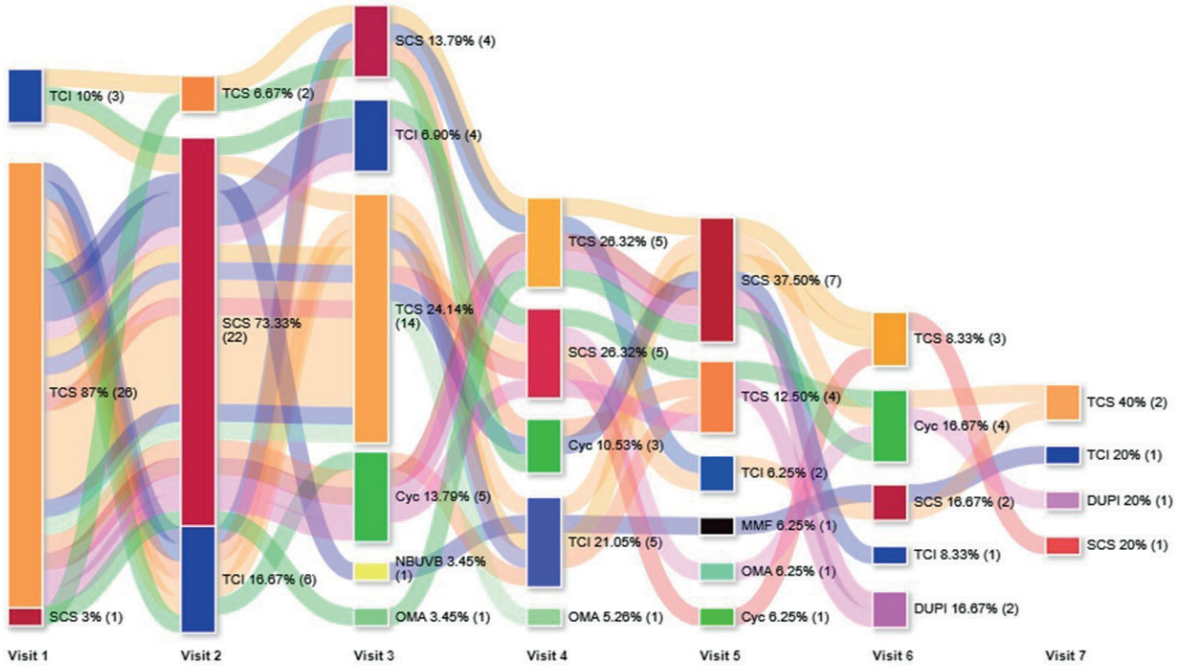

Fig. 3. Treatment journey of children of the study group.

Deciphering the Sankey diagram shows different treatments during the first two visits. First Visit: Most patients used "as-needed" topical corticosteroids, some used as-needed topical calcineurin inhibitors, and a few had a short-term systemic corticosteroid course. Second Visit: Current topical treatments continued, with additional prescriptions of either topical corticosteroids or topical calcineurin inhibitors for those not already using them. The increased use of systemic corticosteroid courses indicates potential challenges with the initial treatment plan.
(CYC: cyclosporine, DUPI: dupilumab, MMF: mycophenolate mofetil, NBUVB: narrow band ultraviolet-B, OMA: omalizumab, SCS: systemic corticosteroid, TCI: topical calcineurin inhibitor, TCS: topical corticosteroid).

patients required more than one intramuscular depot CS injection, which was effective for an average of 3 weeks.

Topical tacrolimus treatment was administered to 56.6% of the patients. Of these, 50% reported an inadequate response, and 20% could not tolerate it due to a burning sensation. Those who benefited from topical tacrolimus showed benefit within 1-2 weeks, but relapse was reported within 7-14 days when treatment was discontinued. The minimum duration of tacrolimus treatment was 9±3.4 days.

Although 17 patients were recommended to use cyclosporine, only 13 patients (43.3%) accepted this treatment and used it for an average of 6 months, and 30.8% (n=4) benefited from this treatment. Reasons for discontinuing included concerns about its long duration (15%) and the desire to avoid using the medication for more than 6 months (80%). One patient (3.3%) experienced hypertrichosis and cellulitis as adverse effects of cyclosporine treatment.

Three patients used dupilumab therapy at their own expense, as it is only reimbursed for patients over 18 years of age in our country. All of these patients had been previously treated with cyclosporine and multiple bursts of SCSs. The patients treated with dupilumab were 7, 15, and 17 years old, respectively (Fig. 4), and their mean objective SCORAD scores before and after treatment were 39.27±18.90 and 11.33±4.16, respectively. Additionally, omalizumab, mycophenolate mofetil, and narrow-band UV treatments were administered to one patient each for durations ranging from 4 to 8 months; however, they yielded minimal benefits.

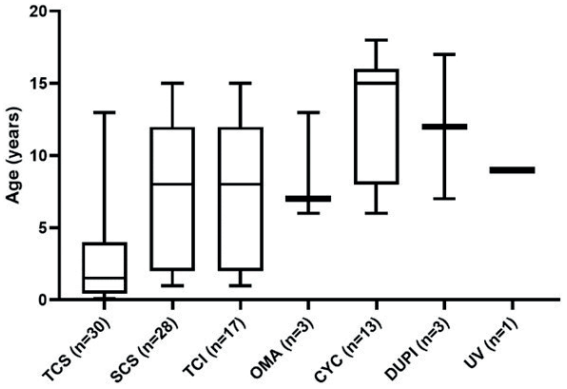

Fig. 4. Age of onset of certain treatments.
(CYC: cyclosporine, DUPI: dupilumab, OMA: omalizumab, SCS: systemic corticosteroid, TCI: topical calcineurin inhibitor, TCS: topical corticosteroid, UV: ultraviolet).

A 16-year-old female patient, despite consistent use of topical calcineurin inhibitors, TCSs, and intermittent SCS treatments, struggled to attain adequate control of the disease. Her symptoms did not respond satisfactorily to a 9-month course of cyclosporine therapy. Due to financial constraints preventing self-payment for dupilumab, the medical council chose to initiate treatment with a JAK inhibitor, specifically baricitinib. Unfortunately, the Ministry of Health declined approval for this treatment due to the patient's age. Consequently, despite the initial intention for the patient to adhere to topical treatments until reaching the age of 18 years, she successfully pursued legal action against the social security agency and transitioned to a conventional dupilumab treatment protocol, thereby achieving effective disease control.

Discussion

AD is one of the most prevalent childhood dermatologic conditions.[1] While many cases of AD can be effectively managed through topical therapies and daily skincare routines, a subset of patients require systemic treatment.[5,13] All patients were advised to follow a proactive treatment plan incorporating both TCS and calcineurin inhibitors, which proved beneficial during its application. However, low compliance emerged as a result of the demanding daily application to extensive body areas, creating challenges for both the patient and their family over time. The regimen was considered unsustainable due to the development of resistance and a decline in compliance.

This study documented the treatment experiences of pediatric and adolescent AD patients who required systemic therapies. Our findings highlight the substantial challenges faced by this patient group, characterized by high healthcare utilization, repeated SCS usage, limited benefit from available systemic treatments, and exploration of alternative/complementary therapies, a reflection of the unmet medical needs experienced by patients and their caregivers. These results underscore the pressing need for further research and consideration regarding the treatment of severe pediatric and adolescent AD patients and a clear demand for more effective and accessible treatment options tailored to this specific population.

Epidemiological insights regarding pediatric AD in Türkiye are limited. A previous multicenter study reported a cumulative prevalence of 8.1% in schoolchildren aged 9-11 years, with a point prevalence of 3.6%. Additionally, 4.3% of children with AD reported intermittent use of SCSs, and 1.4% reported regular SCS treatment.[14] This current study, conducted nearly two decades after the initial epidemiological study, reaffirms the presence of a subgroup of patients burdened by significant challenges and unmet needs. This study marks the first comprehensive exploration of the treatment journeys of pediatric and adolescent AD patients requiring systemic interventions in Türkiye.

Effective management of severe AD typically necessitates a comprehensive, multidisciplinary approach guided by dermatologists or allergists.[13,15,16] Such an approach is crucial for developing personalized treatment plans that address the unique and evolving needs of each patient. Recent advancements in therapies, such as systemic immunosuppressive medications or

biologic agents, have redefined the treatment landscape for severe AD.[17-21] These therapies have not only significantly improved healthcare utilization, disease burden, individual self-esteem, and the quality of life for patients and their caregivers but have also challenged the traditional definition of severe AD, which was based on a limited response to available treatments.

However, the high cost and complex regulatory requirements associated with these emerging therapies pose challenges for healthcare systems. The optimal approach is to incorporate these therapies into healthcare systems while implementing appropriate controls and regulations, ensuring access only for those who genuinely require them. Nonetheless, concerns about the capacity of certain countries to effectively regulate medical practices and industrial activities have led to a hesitancy toward blanket approval. This approach effectively overlooks the minority of patients with urgent needs for these treatments, and healthcare systems struggling to control pharmaceutical promotional efforts may miss valuable opportunities. Prioritizing the patients' needs while balancing accessibility to innovative therapies with cost considerations is of utmost importance.[22]

Another significant aspect of this study involves documenting the characteristics of pediatric and adolescent patients with severe AD. An important finding is that nearly half of our patients exhibited atopic respiratory comorbidities, including asthma and allergic rhinitis. Additionally, almost 70% had aeroallergen sensitization, 16.6% malassezia, and 40% had a food allergy, some of which resolved over time. These findings distinguish our study, in part, from previous investigations on severe AD.[23-26] Our study uncovered a high prevalence of aeroallergen sensitization (70%) and current food allergy (16.6%) among participants with AD. This contrasts with a multicenter study by Illi et al., where reported rates were 40% and 37%, respectively.[26] This disparity underscores potential heterogeneity in AD presentation across diverse populations. In our own research group, a separate study found a food allergy prevalence of 39% among children with AD, indicating that variability in prevalences can also exist within populations.[23] Those differences may be attributed to patient allocation from an allergy clinic.

In this descriptive study, cyclosporine-A was the only systemic treatment with proven efficacy, and approximately half of the patients opted for this treatment. However, only 30% of them achieved the desired response. Omalizumab, mycophenolate mofetil, and narrow-band UV were also attempted as alternative options, but they showed limited effectiveness. Agents with established efficacy, such as JAK inhibitors and dupilumab, could not be prescribed before the age of 18 due to a lack of reimbursement. Based on this rationale, during the study period, three patients initiated dupilumab treatment through self-payment, while one patient commenced drug therapy by taking legal action against the social security institution.

In conclusion, the findings of this first-of-its-kind study highlight the significant burden experienced by pediatric and adolescent patients with AD requiring systemic treatment in Türkiye, including high healthcare utilization, multiple systemic corticosteroid use, and unmet needs. Additionally, there is a need for more effective and accessible treatments for this patient population.

Ethical approval

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The reason for not having family or patient consent should be written because it is a retrospective study. The study protocol received ethical approval from the Institutional Review Board of Hacettepe University (Approval Number: GO 21/871).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: BES, data collection: DIG, HU, ESA, OS, UMS, SEE; analysis and interpretation of results: DIG, BES; visualization: DIG, BES, draft manuscript preparation: BES, DIG, OS, UMS, SEE. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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