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ORIGINAL RESEARCH ARTICLE

Dupilumab Treatment in Children Aged 6–11 Years With Atopic Dermatitis: A Multicentre, Real-Life Study

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Abstract

Background The management of paediatric atopic dermatitis (AD) is challenging, mostly relying on emollients and topical corticosteroids. Dupilumab, a fully human monoclonal antibody, has been recently approved for the treatment of children aged 6–11 years with moderate-to-severe AD not adequately controlled with topical therapies or when those therapies are not advisable.

Objectives The aim of this study was to evaluate in real life the effectiveness and safety of dupilumab in the treatment of children aged from 6 to 11 years.

Methods Demographic and clinical data of children aged 6–11 years, affected by moderate-to-severe AD and treated with dupilumab, were retrospectively collected from 24 dermatological and paediatric referral centres. Dupilumab was administered subcutaneously at an induction dose of 300 mg on day (D) 1, followed by 300 mg on D15 and 300 mg every 4 weeks. Disease severity was assessed at baseline and after week 2 (W2), W4 and W16 of dupilumab therapy using Eczema Area Severity Index (EASI), Pruritus Numerical Rating Scale (P-NRS) and Sleep NRS (S-NRS) and Children's Dermatology Life Quality Index (c-DLQI) score.

Results A total of 55 AD children (24 males [43.64%], 31 females [56.36%]; mean age 9.35 ± 1.75 years) were included. A significant improvement in EASI score, P-NRS, S-NRS and c-DLQI was observed from baseline to W16 of treatment with dupilumab. In particular, at W16 the proportion of patients achieving EASI75 was 74.54%. Moreover, at the same timepoint a significant mean percentage reduction for P-NRS, S-NRS and c-DLQI was also observed (68.39%, 70.22% and 79.03%, respectively).

Conclusions Our real-life data seem to confirm the effectiveness of dupilumab in paediatric patients on all disease aspects, including extent and severity of signs, intensity of symptoms, sleep and QoL, with a good safety profile.

1 Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease in infants and children, appearing within 6 months in 45%, under the age of 1 year in 60% and within the first 5 years in 89% of all the cases [1]. A recent analysis in children aged 6–11 years showed a prevalence of up to 20%; severe AD accounted for up to 8% of cases [2]. AD negatively impacts the quality of life of both children and their families in health-related aspects such as physical, psychosocial and mental functioning [3]. Treatment of children affected by AD can be challenging, especially in moderate-to-severe cases. Indeed, in paediatric patients, AD management mostly relies on emollients and topical corticosteroids (TCs). TCs should be used with caution in children because their body surface area to weight ratio is higher than in adults; as a result, they have a high degree of drug

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Key Points

The management of paediatric atopic dermatitis (AD) is challenging, mostly relying on emollients and topical corticosteroids. Thus, new therapies are required for severe cases.

Dupilumab has been recently approved for the treatment of children aged 6–11 years with moderate-to-severe AD. However, real-life data on the effectiveness and safety of dupilumab in children are scant.

Our multicentre study shows the effectiveness and safety of dupilumab in paediatric patients.

absorption [4]. For this reason, the potential for both cutaneous and systemic side effects, including possible hypothalamic-pituitary-adrenal axis suppression, should be considered [5]. Alternatively, topical calcineurin inhibitors (TCIs), tacrolimus and pimecrolimus, can be used, particularly in sensitive skin sites, such as the face and skin folds [5]. However, access to these drugs is often restricted by payers, and is reserved for children aged > 2 years [5]. Phototherapy is rarely used in children; however, it is not contraindicated, and its use depends on feasibility and equipment (narrowband UVB) [6]. When AD is inadequately controlled with topical therapies or phototherapy, the treatment options in children are limited to short-term systemic corticosteroids (SCs) and off-label drugs (cyclosporine, methotrexate, or azathioprine). However, the use of systemic drugs in AD management is challenging, requiring continuous monitoring due to the risk of potential systemic adverse events (AEs) [6–10].

Dupilumab is a fully human monoclonal antibody that inhibits the subunit α of the interleukin (IL)-4 receptor shared by IL-4 and IL-13. These cytokines are pivotal in the pathogenesis of atopic diseases [11]. Dupilumab is approved for the treatment of moderate-to-severe AD, asthma and chronic sinusitis with nasal polyps. Recently, based on the results of the phase III trial LIBERTY AD PEDS [12], the European Medicines Agency approved dupilumab for the treatment of children aged 6–11 years with moderate-to-severe AD not adequately controlled with topical therapies or when those therapies are not advisable [13]. Dupilumab is also approved by the US Food and Drug Administration for children aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable [14].

The aim of this multicentre, retrospective, observational study was to evaluate in real life the effectiveness and safety of dupilumab in the treatment of children aged from 6 to 11 years.

2 Patients and Methods

Data for children aged 6–11 years and affected by moderate-to-severe AD treated with dupilumab were retrospectively collected from 24 dermatological and paediatric referral centres homogeneously distributed in Northern, Central and Southern Italy. AD diagnosis was performed by a dermatologist based on clinical presentation, personal history and Hanifin and Rajka criteria. Dupilumab was prescribed through a Managed Access Programme (MAP) run by Sanofi-Regeneron® and after approval by the Ethics Committee from May to September 2021. Inclusion criteria were age from 6 to 11 years; disease inadequately controlled with topical conventional approved therapies; Eczema Area and Severity Index (EASI) ≥ 24, or one of the following characteristics: (i) involvement of sensitive areas (face, neck, hands, genitals); (ii) Pruritus Numerical Rating Scale (P-NRS) ≥ 7; (iii) Children's Dermatology Life Quality Index (c-DLQI) score ≥10. These criteria establish appropriateness of patient enrolment in the dupilumab drug prescription programme according to the Italian Medical Agency. Dupilumab was administered subcutaneously at an induction dose of 300 mg on day (D)1, followed by 300 mg on D15 and 300 mg every 4 weeks (Q4W). Based on the physician's assessment of unsatisfactory clinical response, the dose could have been increased to 200 mg Q2W. Patients were allowed to continue using topicals, moisturizers and systemic treatments for AD.

The following demographic and clinical data were recorded: age, sex, medical history, clinical phenotype of AD, comorbidities (atopic and non-atopic), concomitant medications or procedures and adverse events (AEs). Disease severity was assessed at baseline and after week 2 (W2), W4 and W16 of dupilumab therapy using EASI (range 0–72), P-NRS and sleep (S)-NRS (range 0–10) evaluated as peak score during the past 7 days and c-DLQI score (range 0–30). AEs were routinely investigated at each visit. Only consecutive patients with an observational period of at least 16 weeks were included in the study.

Descriptive statistics were calculated for each demographic and clinical variable, using frequencies and percentages for categorical variables and mean ± standard deviation (SD) for continuous ones. GraphPad Prism software (v.8.0; GraphPad Software Inc. La Jolla, CA, USA) was used for all statistical analyses. The Mann-Whitney test and Fisher test were used as appropriate to calculate statistical differences. A p-value of < 0.05 was considered significant.

3 Results

A total of 55 children with AD (24 males [43.64%], 31 females [56.36%]; mean age 9.35 ± 1.75 years) were treated with dupilumab during the reference period. None of them had discontinued the drug; therefore, they all were included in the study. Patients' demographic and clinical baseline characteristics are reported in Table 1. The mean age at symptom onset was 1.86 ± 1.72 years. Of the 55 children, 23 (41.82%) developed AD within the first year of age, 26/55 (47.27%) between 2–6 years and 6/55 (10.91%) after 6 years of age. Flexural dermatitis was the most frequent clinical phenotype and was observed in 25/55 (45.45%) patients, followed by generalized eczema (22/55; 40.00%), nummular eczema (6/55; 10.91%), prurigo nodularis (1/55; 1.82%) and erythroderma (1/55; 1.82%). Current atopic comorbidities were recorded in 36/55 (65.45%) patients (rhinitis [25/55; 45.45%], asthma [20/55; 36.36%], conjunctivitis [11/55; 20.00%] and food allergy [7/55; 12.73%]). Other comorbidities included attention deficit hyperactivity disorder (5/55; 9.09%), coeliac disease (2/55; 3.63%), von Willebrand disease (1/55; 1.82%) and primary immunodeficiency associated with Hartnup disease (1/55; 1.82%). AD family history was reported by 29/55 (52.73%) children. Before enrolment, all the patients had received at least one topical treatment for AD; 41/55 (74.55%) had been treated with TCs and 27/55 (49.09%) with TCIs. Regarding systemic therapies, 36/55 (65.45%) patients had received at least one systemic treatment for AD; 24/55 (43.64%) children had received SCs and 9/55 (16.36%) phototherapy (narrow-band UVB). AD off-label treatment had been prescribed in 18/55 (32.73%) subjects—cyclosporine A (CsA) in 14/55 (25.45%) and methotrexate in 4 (7.27%).

In our cohort, 9/55 (16.36%) patients had an EASI score < 24 (19.65 ± 4.65), but with a high impact on quality of life, as assessed by c-DLQI, P-NRS and S-NRS mean scores of 26.98 ± 2.28, 9.02 ± 0.21 and 8.56 ± 1.43, respectively. Furthermore, all the enrolled patients had AD localization on the face and 5/9 (55.56%) on the hands.

Table 1 Demographic and clinical baseline characteristics of AD patients (6–11 years old) treated with dupilumab ($n = 55$)

Variable	Value
Age (y), mean ± SD	9.35 ± 1.75
Sex, male, *n* (%)	24 (43.64)
AD onset (y), mean ± SD	1.86 ± 1.72
Weight (kg), mean ± SD	28.71 ± 12.43
Height (m), mean ± SD	1.31 ± 0.16
Body mass index, mean ± SD	22.07 ± 5.75
AD family history, *n* (%)	
Atopic dermatitis	26 (47.27)
Conjunctivitis/rhinitis/asthma	19 (34.55)
AD phenotype, *n* (%)	
Lichenified/exudative flexural dermatitis	25 (45.45)
Generalized eczema	22 (40.00)
Nummular dermatitis	6 (10.91)
Prurigo nodularis	1 (1.82)
Erythroderma	1 (1.82)
Clinical scores, mean ± SD	
EASI score	35.6 ± 15.49
DLQI score	21.51 ± 6.10
Peak score on NRS for pruritus	8.86 ± 1.03
Atopic comorbidities, *n* (%)	
Rhinitis	25 (45.45)
Asthma	20 (36.36)
Conjunctivitis	11 (20.00)
Food allergy	7 (12.73)
Other comorbidities, *n* (%)	
Attention deficit hyperactivity disorder	5 (9.09)
Coeliac disease	2 (3.63)
Von Willebrand disease	1 (1.82)
Primary immunodeficiency associated to Hartnup disease	1 (1.82)
Previous systemic treatments for AD, *n* (%)	
Systemic corticosteroids	24 (43.64)
Cyclosporine	14 (25.45)
Phototherapy	9 (16.36)
Methotrexate	4 (7.27)
Previous topical treatments for AD, *n* (%)	
Emollients	55 (100)
Topical corticosteroids	41 (74.55)
Topical calcineurin inhibitors	27 (49.09)

AD atopic dermatitis, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *NRS* numerical rating scale, *SD* standard deviation

3.1 Effectiveness Parameters

A significant improvement in EASI score, P-NRS, S-NRS and c-DLQI was observed from baseline to W16 of treatment with dupilumab (Fig. 1). The mean EASI score at baseline was 35.6 ± 15.49 and reduced to 18.29 ± 10.98 at W2 ($p = 0.209$; mean percentage reduction 48.62%), 10.55 ± 10.39 at W4 ($p < 0.001$; mean percentage reduction 70.36%) and 7.98 ± 8.78 at W16 ($p < 0.001$; mean percentage reduction 77.58%). Overall, at W16 all the patients reached 50% reduction in EASI score (EASI-50), 74.54% (41/55) reached EASI-75 and 9.09% (5/55) EASI-90. P-NRS had a mean value of 8.86 ± 1.03 at baseline, 5.02 ± 2.11 at W2 ($p < 0.0001$; mean percentage reduction 43.45%), 3.21 ± 2.11 at W4 ($p < 0.0001$; mean percentage reduction 63.75%) and 2.8 ± 1.99 at W16 ($p < 0.0001$; mean percentage reduction 68.39%). As reported in Fig. 1, a

significant P-NRS reduction was also observed from W2 to W4 and W16 (<0.001). The mean S-NRS also showed a significant reduction from baseline to timepoint (8.16 ± 2.06 at baseline, 4.3 ± 2.49 at W2 [$p < 0.0001$; mean percentage reduction of 47.3%], 2.34 ± 2.52 at W4 [$p < 0.0001$; mean percentage reduction of 71.32%] and 2.43 ± 2.25 at W16 ($p < 0.0001$; mean percentage reduction of 70.22%]). Also, for S-NRS score we observed a statistically significant reduction ($p < 0.001$) from W2 to W4 and W16, respectively (Fig. 1). A marked improvement has also been observed for c-DLQI, with a baseline value of 21.51 ± 6.10 versus 8.13 ± 5.53 at W2 ($p < 0.0001$; mean percentage reduction of 62.2%), 5.17 ± 4.92 at W4 ($p < 0.0001$; mean percentage reduction of 76.03%) and 4.1 ± 4.38 at W16 ($p < 0.0001$; mean percentage reduction of 79.03%). No statistically significant differences were found for any of the studied parameters between W4 and W16, although a small improvement was observed for all the parameters apart from S-NRS, which remained stable over time.

TCs and/or TCIs were used at baseline by 60.00% (33/55) and 47.27% (26/55) of patients, respectively. After 16 weeks of treatment, TCs dropped out by 72.73% (24/33; p = ns) of patients, while TCIs were stopped by 73.08% (19/26; p = ns) of patients. SCs and CSA were used in 21/55 (38.18%) patients at baseline and were stopped in all these patients during the 16 weeks of treatment with dupilumab; no relapse of the disease was recorded in any of these patients. No patients required an increase of the dupilumab dose.

3.2 Safety Profile

Seven out of 55 (12.73%) patients experienced at least one AE during the 16-week treatment. In our cohort, three (5.45%) patients were diagnosed with conjunctivitis at baseline, while two (3.64%) subjects were diagnosed with dupilumab-associated conjunctivitis occurring during the observation period. Of note, the diagnosis of conjunctivitis at baseline and on-study was made by an ophthalmologist. On average, conjunctivitis occurred after 6.43 ± 4.98 weeks, and was successfully treated with eye drops containing TCs. None of the conjunctivitis at baseline significantly worsened during dupilumab treatment in the three patients. Other common AEs were injection-site reaction (3/55; 5.25%) and headache (2/55; 3.64%). Asymptomatic SARS-CoV-2 infection occurred in 4/55 (7.27%) children, on average, after

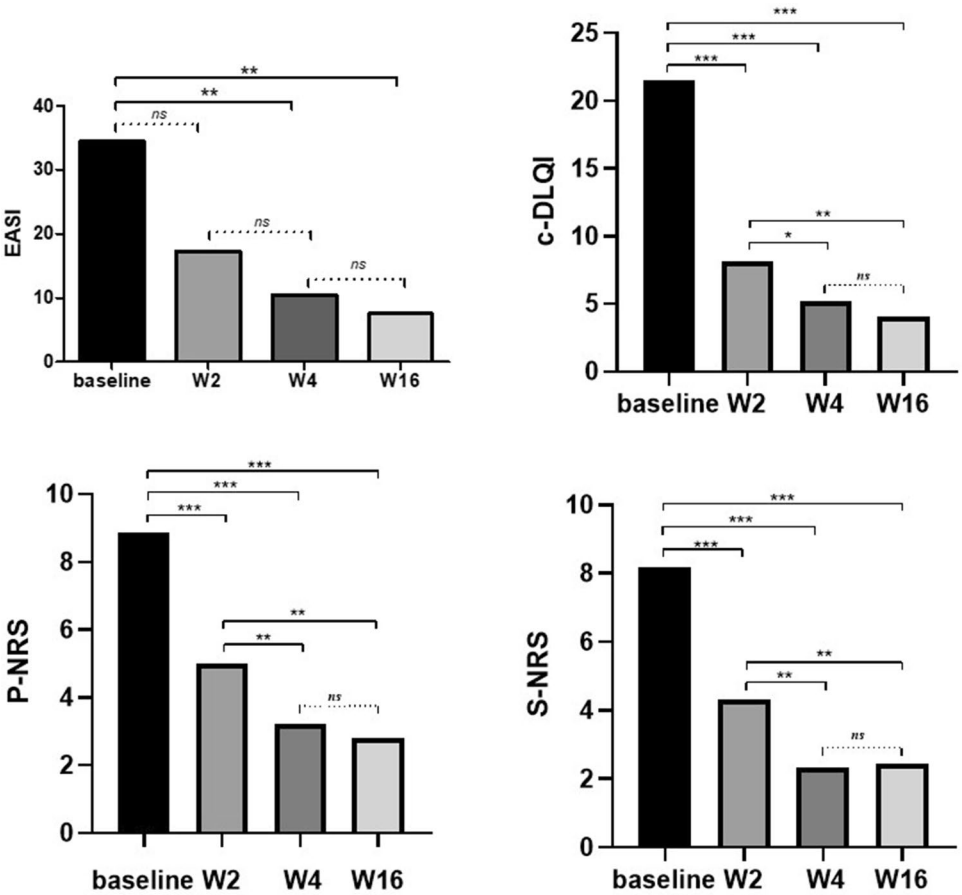

Fig 1 Mean values of EASI, P-NRS, S-NRS and c-DLQI pre- and post-dupilumab treatment in children with atopic dermatitis aged from 6 to 11 years. Mean values of EASI (Eczema Area and Severity Index), S-NRS (Sleep Numerical Rating Scale), P-NRS (Pruritus Numerical Rating Scale) and c-DLQI (Children's Dermatology Life Quality Index) for the study population at baseline and after week 2 (W2), W4 and W16 of dupilumab treatment. Statistical significance was assessed by The Mann–Whitney test and Fisher test: ***$p < 0.0001$, **$p < 0.001$, *$p < 0.005$; *ns* not significant

11.22 ± 4.06 weeks of treatment; these patients continued dupilumab treatment with regular course of infection.

4 Discussion

Recent profiling studies in infants, young children and adolescents affected by AD showed that their skin T helper (Th) cells are polarized in Th2 and Th17 axis, with the absence of the Th1 upregulation seen in adults with AD [15, 16]. Furthermore, paediatric patients with early-onset moderate-to-severe AD already show systemic signs of inflammation within months of onset and before chronic disease develops [15]. These data suggest the need for early intervention in paediatric AD to prevent disease chronicity and perhaps the development of atopic comorbidities and other associated disorders [15]. In this context, it is extremely important to evaluate the effectiveness and safety of immunomodulating drugs in age-specific clinical trials and in real-life studies.

The effectiveness and safety of dupilumab in children was first investigated by Igelman et al. in a multicentre, retrospective review evaluating 124 children who were prescribed off-label dupilumab (dosing range 4–15.5 mg/kg for the loading dose and 2.0–15.3 mg/kg every other week for maintenance) for moderate-to-severe AD. The authors showed that comorbidities, treatment response and AEs were comparable to those in previous adolescent and adult trials supporting dupilumab response and safety in children [17]. These promising results were confirmed by a 3-month multicentre French study enrolling 80 children receiving dupilumab for moderate-to-severe AD, which showed a statistically significant improvement in SCORAD and Investigator Global Assessment (IGA) at 3 months compared with baseline (SCORAD: 21.8 ± 13.8 vs 53.9 ± 18.5; $p < 0.0001$; IGA: 1.3 ± 0.8 vs 3.5 ± 0.7; $p < 0.0001$). As regards the safety, injection-site reactions were the main AE reported ($n = 14$, 17.5%), followed by conjunctivitis ($n = 9$, 11.3%). Moreover, AEs led to treatment discontinuation in three (3.8%) patients. No serious AEs were collected [18].

To the best of our knowledge, this is the first multicentre, Italian real-life study on dupilumab treatment in children with AD aged from 6 to 11 years. The effectiveness of dupilumab was excellent and showed higher results than that observed in the double-blind, 16-week, phase III trial LIBERTY AD PEDS (ClinicalTrials.gov identifier: NCT0335914) [12]. In this clinical trial, a statistically significant improvement was assessed in both the Q4W and Q2W dupilumab + TCs groups compared with placebo + TCs [12]. In particular, 69.7%, 67.2% and 26.8% of patients receiving dupilumab Q4W, dupilumab Q2W or placebo reached EASI-75, respectively. In our cohort, 74.54% of patients achieved EASI-75 at W16. Of note, all patients received dupilumab Q4W. These results are in line with other real-life studies in adolescents and adults [19–22].

The overall effectiveness results in an improvement in AD signs and symptoms such as itch, which is the central and most burdensome symptom of AD directly interfering with daily activities [23]. From baseline to W16 we observed a mean percentage reduction of 68.39% in P-NRS, higher than the 54.6% reduction reported in a pivotal study [12]. Furthermore, in our cohort, relevant decreases in itch severity have been associated with sleep improvement with a mean percentage reduction of 70.22% in S-NRS at W16. Guidelines list sleep as a critical aspect of disease control, also in relation to longitudinal studies investigating the impact of childhood sleep disturbance and suggesting an increased risk of anxiety, inattention and impulsivity [5, 24, 25]. Indeed, compared with peers without AD, patients with AD have a greater incidence of behavioural issues, disrupted family dynamics and anxious parenting [26]. They often face teasing and bullying from their peers due to negative misconceptions or misinformation regarding their condition, and this stigmatization can have detrimental effects on their education, extracurricular activities and future workplace productivity [27]. Dupilumab therapy, by improving skin lesions, pruritus and sleep disturbance, also induced a significant improvement in the quality of life (QoL) of these children as measured through c-DLQI score (mean percentage reduction of 79.03%).

Compared with the baseline, the improvement was already significant at W4 for EASI, and even at 2 weeks for P-NRS, S-NRS and c-DLQI. This data seems to confirm a particular rapidity of action of the drug in children. On the other hand, the further improvement observed from W4 to W16, albeit observed for all parameters evaluated apart from S-NRS, was not significant. However, this trend at least indicates that the improvement is persistent over time, even if longer-term studies are needed. Finally, we observed a favourable safety profile of dupilumab in children aged 6–11 years in line with previous studies in children, adolescents and adults with moderate-to-severe AD [12, 19–22, 28–32]. Injection-site reactions and conjunctivitis were the most common AEs. No dupilumab-related events of serious infection or systemic hypersensitivity reaction were reported.

This real-life study has some limitations; the small sample size precluded a correlation of sex, age, disease onset and clinical phenotype with the response to dupilumab and an observation period of 16 weeks may be too short to evaluate the drug's effectiveness and AE occurrence.

5 Conclusions

To our knowledge, this is the first multicentre study evaluating targeted biologic therapy with dupilumab in real life on a large cohort of children aged 6–11 years with moderate-to-severe AD. Our data seem to confirm the effectiveness of dupilumab in all disease aspects, including extent and severity of signs, intensity of symptoms, sleep and QoL. The safety profile in this age group is in line with previous studies in adults and adolescents.

Declarations

Funding None.

Conflicts of interest M.N. acted as speaker, consultant and advisory board member for Sanofi, AbbVie, LEO Pharma and Novartis, Eli Lilly; G.F. has been principal investigator in clinical trials sponsored by and/or has received personal fees from AbbVie, Abiogen, Almirall, Celgene, Eli Lilly, LEO Pharma, Novartis, Sanofi and UCB; I.N. reports personal fees for participation in advisory boards from Sanofi, Novartis, Eli Lilly; L.S. has been principal investigator in clinical trials sponsored by and/or and has received personal fees for participation in advisory boards from AbbVie, LEO Pharma, Novartis and Sanofi, outside the submitted work; A.C. received consulting fees from AbbVie, Almirall, Eli Lilly, Janssen, Novartis, LEO Pharma, Sanofi, Genzyme and acted for Sanofi, AbbVie and Eli Lilly; K.H. reports personal fees from AbbVie and Novartis, outside the submitted work; A.L. acted as a speaker, consultant and advisory board member for Sanofi, Chiesi, GlaxoSmithKline and Novartis; P.P. acted as speaker for Sanofi; C.P. acted as investigator, speaker, consultant and advisory board member for AbbVie, Amgen, Eli Lilly, LEO Pharma, Novartis, Pfizer, Pierre Fabre and Sanofi; V.B., V.P., F.A., G.M., R.D.P., E.V.D.B., L.D., L.B. A.D.G, E.D.D., V.M., V.D.L., F.D., M.G., S.M., S.L., L.M., M.O., E.P., A.P., V.P., T.P., T.B., L.P., R.S., S.T., L.M., T.P., P.Z. report no conflicts of interest.

Ethics approval Ethics committee approval was obtained for this retrospective study; code 138/21.

Consent to participate Patients and their parents gave written informed consent for participation in the study.

Consent to publish Patients and their parents gave written informed consent for publication of their case details.

Data availability statement Data that support the findings of this study are available from the corresponding author, MN, upon reasonable request.

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References

1. Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy. 2015;70:836–45.
2. Silverberg JI, Barbarot S, Gadkari A, et al. Atopic dermatitis in the pediatric population. A cross sectional, international epidemiologic study. Ann Allergy Asthma Immunol. 2021;126:417–28.
3. Na CH, Chung J, Simpson EL. Quality of life and disease impact of atopic dermatitis and psoriasis on children and their families. Children (Basel). 2019;6(12):133.
4. Axon E, Chalmers JR, Santer M, et al. Safety of topical corticosteroids in atopic eczema: an umbrella review. BMJ Open. 2021;11(7): e046476.
5. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71(1):116–32.
6. Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. J Eur Acad Dermatol Venereol. 2018;32:850–78.
7. Drucker AM, Eyerich K, de Bruin-Weller MS, et al. Use of systemic corticosteroids for atopic dermatitis: international Eczema council consensus statement. Br J Dermatol. 2018;178:768–75.
8. Lebwohl M, Alexis AF, Beck LA, et al. Systemic therapies for moderate-to-severe atopic dermatitis: expert perspectives in practice. J Drugs Dermatol. 2019;18:122–9.
9. Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. J Allergy Clin Immunol. 2013;132:774-774.e6.
10. Totri CR, Eichenfield LF, Logan K, et al. Prescribing practices for systemic agents in the treatment of severe pediatric atopic

dermatitis in the US and Canada: the PeDRA TREAT survey. J Am Acad Dermatol. 2017;76:281–5.
11. Regeneron pharmaceuticals. DUPIXENTVR prescribing information. Tarrytown, NY; 2018 October. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s007lbl.pdf
12. Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol. 2020;83(5):1282–93.
13. https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761055s042lbl.pdf
15. Brunner PM, He H, Pavel AB, et al. The blood proteomic signature of early-onset pediatric atopic dermatitis shows systemic inflammation and is distinct from adult long-standing disease. J Am Acad Dermatol. 2019;81(2):510–9.
16. Esaki H, Brunner PM, Renert-Yuval Y, et al. Early-onset pediatric atopic dermatitis is T_H2 but also T_H17 polarized in skin. J Allergy Clin Immunol. 2016;138(6):1639–51.
17. Igelman S, Kurta AO, Sheikh U, et al. Off-label use of dupilumab for pediatric patients with atopic dermatitis: a multicenter retrospective review. J Am Acad Dermatol. 2020;82(2):407–11.
18. Lasek A, Bellon N, Mallet S, et al. Effectiveness and safety of dupilumab in the treatment of atopic dermatitis in children (6–11 years): data from a French multicenter retrospective cohort in daily practice. J Eur Acad Dermatol Venereol. 2022. https://doi.org/10.1111/jdv.18450.
19. Stingeni L, Hansel K, Antonelli E, Bello GD, Patruno C, Napolitano M, Fabbrocini G, Grieco T, Pellacani G, Fargnoli MC, et al. Atopic dermatitis in adolescents: effectiveness and safety of dupilumab in a 16-week real-life experience during the COVID-19 pandemic in Italy. Dermatol Ther. 2021;34(5): e15035.
20. Hansel K, Patruno C, Antonelli E, Dal Bello G, Napolitano M, Fabbrocini G, Grieco T, Pellacani G, Fargnoli MC, Esposito M, et al. Dupilumab in adolescents with moderate to severe atopic dermatitis: a 32-week real-world experience during the COVID-19 pandemic. Clin Exp Dermatol. 2021. https://doi.org/10.1111/ced.14862.
21. Patruno C, Fabbrocini G, Longo G, et al. Dupilumab for Atopic Dermatitis of the Elderly (DADE) Study Group. Effectiveness and safety of long-term dupilumab treatment in elderly patients with atopic dermatitis: a multicenter real-life observational study. Am J Clin Dermatol. 2021;22(4):581–6.
22. Patruno C, Napolitano M, Argenziano G, et al. Dupilumab therapy of atopic dermatitis of the elderly: a multicentre, real-life study. J Eur Acad Dermatol Venereol. 2021;35(4):958–64. https://doi.org/10.1111/jdv.17094.
23. Napolitano M, Ferrillo M, Patruno C, Scalvenzi M, D'Andrea M, Fabbrocini G. Efficacy and safety of dupilumab in clinical practice: one year of experience on 165 adult patients from a tertiary referral centre. Dermatol Ther (Heidelb). 2021;11(2):355–61. https://doi.org/10.1007/s13555-021-00505-z.
24. Ali F, Vyas J, Finlay AY. Counting the burden: atopic dermatitis and health-related quality of life. Acta Derm Venereol. 2020;100(12):161.
25. Cook F, Conway LJ, Giallo R, Gartland D, Sciberras E, Brown S. Infant sleep and child mental health: a longitudinal investigation. Arch Dis Child. 2020;105(7):655–60.
26. Huhdanpää H, Morales-Muñoz I, Aronen ET, Pölkki P, Saarenpää-Heikkilä O, Paunio T, et al. Sleep difficulties in infancy are associated with symptoms of inattention and hyperactivity at the age of 5 years: a longitudinal study. J Dev Behav Pediatr JDBP. 2019;40(6):432–40.
27. Nguyen CM, Koo J, Cordoro KM. Psychodermatologic effects of atopic dermatitis and acne: a review on self-esteem and identity. Pediatr Dermatol. 2016;33:129–35.
28. Kelly KA, Balogh EA, Kaplan SG, Feldman SR. Skin disease in children: effects on quality of life, stigmatization, bullying, and suicide risk in pediatric acne, atopic dermatitis, and psoriasis patients. Children (Basel). 2021;8(11):1057.
29. Cork MJ, Thaçi D, Eichenfield LF, et al. Dupilumab provides favourable long-term safety and efficacy in children aged ≥ 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. Br J Dermatol. 2021;184(5):857–70.
30. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase III trial. Lancet. 2017;389:2287–303.
31. de Bruin-Weller M, Thaci D, Smith CH, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). Br J Dermatol. 2018;178:1083–101.
32. Colonna C, Zussino M, Monzani NA, Ponziani A, Cavalli R. Treatment of children from 6 to 11 years old affected by moderate-severe atopic dermatitis with dupilumab: a first perspective from a single-center real-life experience in Italy. J Eur Acad Dermatol Venereol. 2022;2:2.

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