ORIGINAL ARTICLE

Moderate-to-severe atopic dermatitis in adolescents treated with dupilumab: A multicentre Italian real-world experience

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Abstract

Background Moderate-to-severe atopic dermatitis (AD) in the adolescence is a high burden disease, and its treatment can be very challenging due to paucity of approved systemic drugs for this age and their side-effects. Dupilumab was recently approved for treatment of adolescent AD.

Objectives A multicentre, prospective, real-world study on the effectiveness and safety of dupilumab in adolescents (aged from ≥12 to <18 years) with moderate-to-severe AD was conducted. The main AD clinical phenotypes were also examined.

Methods Data of adolescents with moderate-to-severe AD treated with dupilumab at label dosage for 16 weeks were collected. Treatment outcome was assessed by EASI, NRS itch, NRS sleep loss and CDLQI scores at baseline and after 16 weeks of treatment. The clinical scores were also evaluated according to clinical phenotypes.

Results One hundred and thirty-nine adolescents were enrolled in the study. Flexural eczema and head and neck eczema were the most frequent clinical phenotypes, followed by hand eczema and portrait-like dermatitis. Coexistence of more than 1 phenotype was documented in 126/139 (88.5%) adolescents. Three patients (2.1%) contracted asymptomatic SARS-CoV-2 infection and 1 of the discontinued dupilumab treatment before the target treatment period. A significant improvement in EASI, NRS itch, NRS sleep loss and CDLQI was observed after 16 weeks of treatment with dupilumab. This outcome was better than that observed in clinical trials. Dupilumab resulted effective in all AD phenotypes, especially in diffuse eczema. Twenty-eight (20.1%) patients reported adverse events, conjunctivitis and flushing being the most frequent. None of patients discontinued dupilumab due to adverse event.

Conclusions Dupilumab in adolescent AD showed excellent effectiveness at week 16 with consistent improvement of all clinical scores. Moreover, dupilumab showed a good safety profile also in this COVID-19 pandemic era.

Received: 18 December 2021; revised: 12 February 2022; Accepted: 23 March 2022

Conflict of Interest

L. S. has been principal investigator in clinical trials sponsored by and/or and has received personal fees for participation in advisory board from Abbvie, LeoPharma, Novartis and Sanofi, outside the submitted work; G.F. has been principal investigator in clinical trials sponsored by and/or and has received personal fees from Abbvie, Abiogen, Almirall, Celgene, Eli-Lilly, Leo Pharma, Novartis, Sanofi and UCB, outside the submitted work; E.N. has been Advisory board member for Sanofi, outside the submitted work; M.N. acted as speaker, consultant and advisory board member for Sanofi, Abbvie, Leo Pharma, Novartis and Lilly, outside the submitted work; F.G. received support for attending meetings and/or travel from Sanofi, outside the submitted work; M.C.F. received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events and for participation on a data safety monitoring board or advisory board from Sanofi, Lilly, Abbvie, Galderma and Pfizer, outside the submitted work; A.O. has been principal investigator in clinical trials sponsored by and/or and has received personal fees from Abbvie, LeoPharma and Sanofi, outside the submitted work; A.C. received consulting fees from Abbvie, Almirall, Biogen, Incyte, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie, Almirall, LeoPharma, Lilly, Janssen, Novartis and Sanofi, outside the submitted work; K.H. reports personal fees from Abbvie and Novartis, outside the submitted work; L.B., E.A., E.S.C., S.M.F, M.O., D.S., M.G., L.B., M.R., A.B.F., A.B., K.P., C.F., M.R., C.P., P.S., F.R., E.E., T.B., L.B., G.P., C.F., M.C., G.M., N.M., G.M. and M.T. report no conflicts of interest.

Funding sources

None.

Introduction

Atopic dermatitis (AD) is a complex disease with an interplay between abnormal immune response, genetic impairment of skin barrier and environmental factors.[1] Global AD prevalence is increasing in all ages: in children up to 20%,[2] while in adults and elderly up to 10%.[2–4] In adolescents (≥12 to <18 years), this prevalence is up to 16.0% worldwide,[5] and the increasing trend was also confirmed in Italy.[6]

In one third of adolescents with AD, the disease is moderate-to-severe [7] and frequently associated with atopic and non-atopic comorbidities.[8] Adolescent AD is characterized by a high disease burden affecting patients' quality of life[9] due to chronic or relapsing course of itchy skin lesions and sleep loss. In addition, adolescent AD is frequently associated with difficulties in building social relationships and in maintaining good school performance, to bullying, depression and anxiety as well as suicidal ideation.[10–12] Treatment of moderate-to-severe adolescent AD can be very challenging. Cyclosporine A (CsA) is the only systemic immunosuppressive drug recommended in Italy for patients ≥16 years old, while methotrexate, azathioprine and mofetil micofenolate are not approved.[13] Dupilumab is an anti-interleukin-4-receptor-α monoclonal antibody blocking signalling of interleukins 4 and 13 and inhibiting the differentiation of naive T cells into T helper (Th) 2 cells. In adolescents, it showed a significant improvement of signs and symptoms at Week 16 in phase 3 randomized, placebo-controlled, clinical trial (R668-AD-1526 LIBERTY AD ADOL, NCT03054428)[14] and phase 2a and subsequent phase 3 open label extension (R668-AD-1412, NCT02407756; R668-AD-1434 LIBERTY AD PED-OLE, NCT02612454),[15] with a good safety profile. In view of that, dupilumab received the EMA (European Medical Agency) and AIFA (Agenzia Italiana del Farmaco) approval on 6

[†]DADA study group are present in Appendix

The patient and their parents in this manuscript have given written informed consent to publication of their case details.

August 2019 and 8 October 2020, respectively, and reimbursement in Italy on 9 December 2020.[16] Real-life data concerning effectiveness and safety of dupilumab in adolescents are rarely reported.[17–19]

Herein, we describe our Italian real-world experience to evaluate the clinical features of 139 AD patients aged from ≥12 to <18 years and the effectiveness and safety of dupilumab in a 16-week prospective observational study.

Methods

Data on adolescents (age from ≥12 to <18 years) with AD treated with dupilumab started from December 2020 to February 2021 in 30 dermatological referral centres homogeneously distributed in Northern, Central and Southern Italy, were collected prospectively. Adolescents were enrolled in the study according to the following inclusion criteria: age ≥ 12 years; diagnosis of AD made by an expert, board-certified dermatologist; Eczema Area and Severity Index (EASI) ≥24 or localization in visible or sensible areas (face, neck, hands or genitalia); or Numeric Rating Scale (NRS) itch ≥7 or Children Dermatology Life Quality Index (CDLQI) ≥10. These treatment criteria are established for patient enrolment in dupilumab drug prescription appropriateness according to the Italian Medical Agency.[20] Dupilumab was administered subcutaneously (SC) at label dosage: for adolescents <60 kg a loading dose of 400 mg (2 x 200 mg SC injections) followed by 200 mg (1 SC injection) Q2W; for adolescents ≥60 kg, a loading dose of 600 mg (2 x 300 mg SC injections) followed by 300 mg (1 SC injection) Q2W. Patients with an observational period of at least 16 weeks were consecutively included in the study.

The following demographic and clinical data were recorded at baseline: age, gender, age of onset and clinical course (childhood or adolescent onset with persistent or relapsing course), clinical phenotype of AD, comorbidities (atopic and non-atopic), concomitant medications or procedures and efficacy outcomes to previous treatments. Disease severity was assessed at baseline and after 16 weeks of dupilumab therapy using EASI score (range 0–72), pruritus and sleep loss NRS score (range 0–10) evaluated as peak score during the past 7 days and CDLQI score (range 0–30). The effectiveness of dupilumab in terms of EASI improvement was also evaluated according to gender, BMI, EASI and total serum immunoglobulin E (IgE; normal ≤150 KU/ml) at baseline, age of onset and clinical course. Moreover, dupilumab effectiveness on EASI improvement, NRS itch and sleep loss score reduction (≥4-point reduction), and CDLQI mean score reduction were evaluated according to clinical phenotypes. At Week 16, adverse events (AEs) and concomitant medications were recorded.

The study protocol was approved by the Ethic Committees of the participating centres. Signed informed consent was obtained from patients' parents. Differences in paired discrete data were tested by Wilcoxon signed rank test, chi-squared test with Yates' continuity correction or Fisher's exact test were used to analyse categorical data. All statistical analyses were performed using IBM-SPSS® version 26.0 (IBM Corp., Armonk, NY, USA, 2019). In all analyses, a two-sided *P*-value ≤0.05 was considered significant.

Results

A total of 139 AD adolescent patients [males 75 (54.0%), mean age 14.9 years; females 64 (46.0%), mean age 15.3 years] treated with dupilumab during the reference period were enrolled in the study. Demographic and clinical baseline characteristics of patients are reported in Table 1. In particular, the mean values of age, weight and BMI were 15.1 years, 60.2 Kg and 22.0 Kg/m^2, respectively. BMI was <25 in 125/139 adolescents (89.9%). Among atopic comorbidities, rhinitis was the most frequent (51.1%), followed by asthma (28.1%), conjunctivitis (25.9%) and food allergy (10.1%). Other main comorbidities were acne (8, 5.8%), obesity (5, 3.6%), depression (3, 2.1%) and diabetes mellitus (2, 1.4%).

Clinical manifestations of AD occurred within the first year of life in 90 patients (64.7%) and after 1 year of life in 49 (35.3%). Among the latter, AD appeared in preschool children (<6 years) in 35 (25.2%), in children aged between 6 and 12 years in 9 (6.5%) and in adolescents (≥12 years) in 5 (3.6%). The prevalent clinical course was persistent in 72.7% with an AD average duration of 12.9 ± 3,39 years (range 2–17 years). Flexural eczema and head and neck eczema were the most frequent clinical phenotypes (84.9% and 84.2%, respectively), followed by hand eczema (49.6%), portrait-like dermatitis (20.1%), diffuse eczema (6.5%), eczema nummulare-like (5.8%), prurigo nodularis-like (2.1%) and erythrodermia (0.7%). The 2 most frequent associations between 2 or more phenotypes were flexural eczema with head and neck eczema and hand eczema in 28.8% and flexural eczema with head and neck eczema in 27.3% (Fig. 1).

Almost all AD adolescents received at least one systemic treatment for AD (97.8%) before enrolment (Table 1). In particular, 126 (90.7%) was treated with antihistamines, 108 (77.7%) with corticosteroids (Cs), 54 (38.9%) with CsA and 28 (20.1%) with phototherapy. All these treatments were prescribed before the availability of dupilumab for adolescent AD in Italy.

According to bodyweight, 65 (46.8%) adolescents received a loading dose of 400 mg followed by 200 mg Q2W and 74 (53.2%) a loading dose of 600 mg followed by 300 mg Q2W. Three patients (2.1%) contracted asymptomatic SARS-CoV-2 infection; among them, a 16-year-old boy discontinued dupilumab treatment before the target treatment period (Week 16). The remaining 138 (99.3%) patients completed the 16-week treatment period.

A significant improvement in EASI, NRS itch, NRS sleep loss and CDLQI was observed after 16 weeks of treatment with dupilumab (Table 2). The mean EASI score at baseline was 26.2 ± 7.7 and significantly reduced to 5.3 ± 4.5 at 16 weeks

Table 1 Demographics and clinical data of 139 adolescents with moderate-to-severe atopic dermatitis

Parameter	Value (min-max)	(%) [DS]
Total	**139**	
Males	75	(54.0)
Age (years)	15.1 (12–17)	[±1.5]
Weight (kg)	60.2 (36–102)	[±10.4]
Height (cm)	165.6 (145–188)	[±0.1]
BMI (kg/m^2)	22.0 (14.8–32.2)	[±3.0]
Atopic comorbidities		
Rhinitis	71	(51.1)
Asthma	39	(28.1)
Conjunctivitis	36	(25.9)
Food allergy	14	(10.1)
Age of onset		
≤1 year	90	(64.8)
>1 year	49	(35.2)
Clinical course		
Persistent	101	(72.7)
Relapsing	38	(27.3)
Phenotypes		
Flexural eczema	118	(84.9)
Head and neck eczema	117	(84.2)
Hand eczema	69	(49.6)
Portrait-like dermatitis	28	(20.1)
Diffuse eczema	9	(6.5)
Eczema nummulare-like	8	(5.8)
Prurigo nodularis-like	3	(2.1)
Erythrodermia	1	(0.7)
Previous systemic treatments		
Antihistamines	126	(90.7)
Corticosteroids	108	(77.7)
Cyclosporine A	54	(38.9)
Phototherapy	28	(20.1)
Methotrexate	1	(0.7)
None	3	(2.2)

BMI, body mass index.

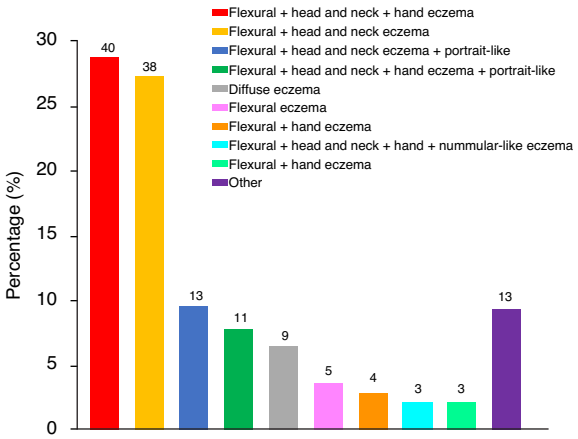

Figure 1 Distribution of atopic dermatitis phenotypes in 139 adolescents.

Table 2 Atopic dermatitis outcome in 138 adolescents at Week 16 of therapy with dupilumab

Parameter	Value [DS]		Δ (%)
	Baseline	Week-16	
AD severity score*			
EASI	26.2 [±7.7]	5.3 [±4.5]	20.9 (79.8)**
CDLQI	14.4 [±6.4]	3.9 [±3.4]	10.5 (72.9)**
NRS sleep loss	6.6 [±2.9]	1.6 [±2.1]	5.0 (75.8)**
NRS itch	8.2 [±1.5]	2.9 [±2.3]	5.3 (64.6)**

AD, atopic dermatitis; CDLQI, Children Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale.
*mean value; **$P < 0.01$.

($P < 0.01$), with a mean percentage reduction of 79.8%. The mean percentage reduction in CDLQI score from baseline (14.4 ± 6.4) to 16 weeks (3.9 ± 3.4) was 72.9% ($P < 0.01$). NRS sleep loss had a mean value of 6.6 ± 2.9 at baseline *vs.* 1.6 ± 2.1 at 16 weeks ($P < 0.01$; mean percentage reduction of 75.8%). The mean NRS itch showed a significant reduction from baseline to timepoint (8.2 ± 1.5 at baseline *vs.* 2.9 ± 2.3 at week 16; $P < 0.01$; mean percentage reduction of 64.6%).

Data on effectiveness of dupilumab in terms of EASI improvement according to gender, BMI, baseline EASI, baseline total serum IgE, age of onset and clinical course are reported in Table 3. Overall, almost all patients (99.3%) reached EASI-50, while EASI-75 and EASI-90 were reached by 64.5% and 33.3% of adolescents, respectively; complete clear skin was achieved by 15.9% of adolescents. According to gender, dupilumab effectiveness resulted higher in females than in males for EASI-75, EASI-90 and EASI-100, reaching statistical significance for EASI-75 ($P < 0.05$). Similarly, dupilumab resulted more effective in patients with baseline BMI < 25, especially for EASI-75 (66.9% *vs* 42.9%). All EASI improvements were higher for adolescents with baseline EASI <24, especially for EASI-100 (27.3% *vs* 12.4%), without statistical significance. Regarding baseline serum total IgE, determined in 118 patients, dupilumab was more effective in adolescents with values in normal range (≤150 KU/ml), especially for EASI-100 (30.0% *vs* 13.6%). Age of AD onset (≤1 year and >1 year) and clinical course (persistent and relapsing) did not influence the therapeutic outcome, even if patients with AD relapsing course had a slightly better response.

Baseline serum total IgE levels were higher than normal range in 88/118 (74.6%) patients. In these adolescents, the mean value decreased in 82/88 (93.2%) from 2215.9 KU/ml to 1329.3 KU/ml at Week 16.

Therapeutic outcome in terms of EASI improvement, NRS itch and sleep loss reduction (≥4-point reduction) according to the 7 most frequent clinical phenotypes is reported in Fig. 2.

Table 3 Dupilumab effectiveness in 138 adolescents with moderate to severe atopic dermatitis at week 16 according to gender, BMI (< or ≥ 25), baseline EASI (< or ≥ 24), serum total IgE at baseline (≤ or > 150 KU/ml) (determined in 118 patients), age of onset (≤ or > 1 year) and clinical course (persistent or relapsing)

Parameters (*n*)	Week 16			
	EASI-50 (%)	EASI-75 (%)	EASI-90 (%)	EASI-100 (%)
All patients (138)	137 (99.3)	89 (64.5)	46 (33.3)	22 (15.9)
Gender				
Male (75)	75 (100)	42 (56.0)	21 (28.0)	10 (13.3)
Female (63)	62 (98.4)	47 (76.6)*	25 (39.7)	12 (19.0)
BMI				
<25 (124)	123 (99.2)	83 (66.9)	42 (33.9)	20 (16.1)
≥25 (14)	14 (100)	6 (42.9)	4 (28.6)	2 (14.3)
Baseline EASI				
<24 (33)	33 (100)	24 (72.7)	13 (39.4)	9 (27.3)
≥24 (105)	104 (99.0)	65 (61.9)	33 (31.4)	13 (12.4)
Baseline serum total IgE (118)				
≤150 KU/mL (30)	30 (100)	24 (80.0)	14 (46.7)	9 (30.0)
>150 KU/mL (88)	87 (98.9)	55 (62.5)	30 (34.1)	12 (13.6)
Age of onset				
≤1 year (89)	89 (100)	60 (67.4)	33 (37.1)	14 (15.7)
>1 year (49)	48 (98.0)	29 (59.2)	13 (26.5)	8 (16.3)
Clinical course				
Persistent (100)	99 (99.0)	63 (63.0)	32 (32.0)	15 (15.0)
Relapsing (38)	38 (100)	26 (68.4)	14 (36.8)	7 (18.4)

BMI, body mass index; EASI, Eczema Area and Severity Index.
*$P < 0.05$.

Diffuse eczema correlated with higher dupilumab efficacy, especially for EASI-90 and EASI-100, while the other clinical phenotypes showed similar therapeutic outcome.

Among topical therapies, Cs and/or immunomodulators (TIMs) (tacrolimus and pimecrolimus) were used at baseline by 71.0% (98/138) and 22.5% (31/138) patients, respectively. After 16 weeks of dupilumab treatment, topical Cs were stopped by 54.1% (53/98) of patients, while TIMs by 35.5% (11/31). Systemic drugs were used in 82 (59.4%) adolescents at baseline, particularly antihistamines (43, 31.2%), Cs (22, 15.9%) and CyA (17, 12.3%). Fifty-seven patients out of the 82 adolescents (69.5%) discontinued systemic therapy during the first month. All adolescents stopped treatment with Cs and CyA during the first 4 weeks; in particular, Cs in 11 at week-1, in 7 at week-2 and in 4 at week-3 (mean: 11.5 days), while CyA in 4 at week-1, 6 at week-2, 5 at week-3 and 2 at week-4 (mean: 15.8 days). Antihistamines were stopped by 18 adolescents (12 at week-1, 4 at week-2 and 2 at week-3), while the remaining 25 (30.5%) adolescents continued them on demand.

Twenty-eight out of 139 (20.1%) adolescents experienced at least one adverse event (AE) during the 16-week treatment. Fifteen (10.8%) were diagnosed with mild-to-moderate conjunctivitis (6 *de novo*, 4 worsening of pre-existent and 5 reappearance of anamnestic conjunctivitis) successfully treated with artificial tears, hyaluronic acid eye drops, topical Cs, CsA or tacrolimus. Other AEs were flushing (5, 3.6%), injection-site reaction (4, 2.9%), fatigue (2, 1.4%), diarrhoea (2, 1.4%), headache (1, 0.7%) and herpes simplex (1, 0.7%). None of the patients discontinued dupilumab due to AEs.

Discussion

AD in adolescents, unlike childhood and adult AD, has been rarely approached from clinical and therapeutic perspectives,[21] even if in this age the disease burden is particularly high due to sleep disturbances, behavioural problems, reduced level of attention in school activities, social isolation, episodes of bullying and problems in the sexual sphere.[10–12,22,23] Therefore, quality of life (QoL) is significantly reduced in adolescents with AD and also in their caregivers, who often experience low sleep quality and deteriorated psycho-emotional state. Moreover, adolescent AD is burdened by a substantial direct and indirect economic impact depending on the disease severity.[9]

Dupilumab is currently the only innovative systemic therapy for moderate-to-severe AD in adolescents and until now only few reports on small case series are available in literature.[17–19,24,25] In this 16-week prospective observational study conducted in 30 Italian Dermatologic Clinics, we evaluated the effectiveness and safety of dupilumab in a large study group of adolescents who started dupilumab immediately after its reimbursement.

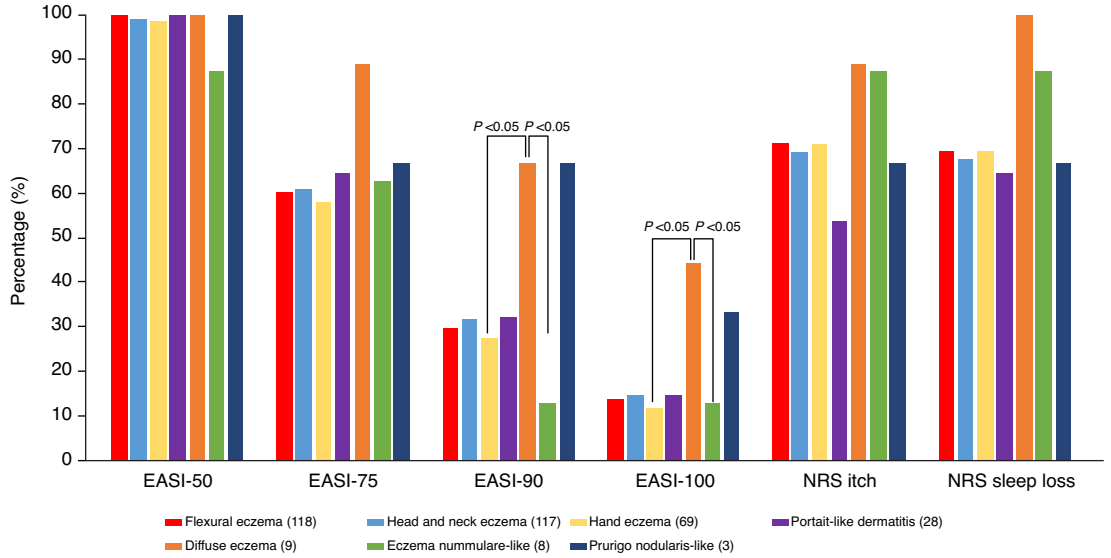

Figure 2 Atopic dermatitis outcome in 138 patients at Week 16 of therapy with dupilumab according to the 7 most frequent clinical phenotypes.

Our patients, with a long-standing AD (mean duration 13.0 years), were mostly normal weight (115/139, 82.7%), while 14 (12.3%) were overweight and obese (11 and 3, respectively). Our data on association of adolescent AD with BMI >25 are in accordance with recent literature,[15,16,26] even if this issue is still debated.[27,28] Atopic comorbidities were present in 85/139 adolescents (61.2%) confirming the high prevalence of other atopic diseases in this setting of AD patients,[15,16,29] while other comorbidities (acne, obesity, depression and diabetes mellitus) were not frequent (15/139, 10.8%). Regarding AD clinical features, we documented coexistence of more than 1 phenotype in most of the adolescents (126/139, 88.5%), with flexural, head and neck, and hand eczema the most 3 frequent (Fig. 1), confirming that adolescent AD is a bridge between childhood and adult AD.[29] In view of the long disease history, almost all patients (136/139, 97.8%) were previously treated with at least one systemic drug (mean number of treatments for patient: 2.3). At baseline, 39 patients were in treatment with Cs (22) and CyA (17) with unsatisfactory results. These systemic drugs were gradually tapered and stopped within 4 weeks in all patients. In particular, Cs were stopped in 5 to 20 days and CyA in 7 to 26 days.

In this multicentre real-life experience on dupilumab in adolescents with moderate-to-severe AD, the effectiveness of dupilumab at Week 16 was excellent (Table 2). EASI change from baseline (79.8%) was significantly higher than that observed in LIBERTY AD ADOL[14] (65.9%) and similar to that observed in LIBERTY AD PED-OLE[15] (81.6%). Also regarding NRS itch and NRS sleep loss scores, an improvement greater than that observed in clinical trials was documented. In fact, our patients showed a 5.3-point reduction in NRS itch score compared with 3.6-point and 3.9-point reduction in LIBERTY AD ADOL[14] and LIBERTY AD PED-OLE,[15] respectively, together with 75.8% reduction in NRS sleep loss, compared with 47.9% reduction in LIBERTY AD ADOL post hoc analysis.[30] Regarding QoL, we documented a reduction (10.5 points) in CDLQI higher than that in LIBERTY AD ADOL[14] (8.5 points).

In terms of improvement from baseline EASI (Table 3), EASI-50 was reached by almost all of our patients (99.3%), substantially higher than that reported in LIBERTY AD ADOL[14] (61.0%) and similar to that reported in LIBERTY AD PED-OLE[15] (97.2%). EASI-75 was achieved by 64.5% of our patients and resulted in between LIBERTY AD ADOL post hoc analysis[30] (41.0%) and LIBERTY AD PED-OLE[15] (69.4%) results. Similarly, EASI-90 (achieved by 33.3% of our patients) was in between LIBERTY AD ADOL[14] (20.8%) and LIBERTY AD PED-OLE[15] (44.4%). Notably, EASI-100 was achieved by 15.9% of our patients, and data are not reported in the clinical trials.

Analysing EASI improvement according to gender and clinical baseline characteristics, we documented a better therapeutic outcome in females than in males. Moreover, our data suggest that low BMI, low EASI, normal serum total IgE and early age of onset may positively influence the effectiveness of dupilumab in terms of EASI-75, EASI-90 and EASI-100 (Table 3). The possible correlation between low BMI and better therapeutic outcome was observed in psoriasis where low BMI frequently correlates with higher PASI percentage response to biologics.[31,32] The correlations observed in our AD patients need to be verified in further studies on adolescents affected by this high burden disease.

In the attempt to predict the therapeutic outcome according to AD clinical features (Fig. 2), all phenotypes showed similar response to dupilumab therapy, except for diffuse eczema in which dupilumab resulted more effective in terms of EASI-90 and EASI-100 compared with hand eczema and eczema nummulare-like.

Effectiveness of dupilumab was also confirmed by the reduction in topical therapies, especially for Cs stopped in 54.1% of our patients and by the discontinuation in all patients of systemic Cs and CyA within 3 (mean: 11.5 days) and 4 weeks (mean: 15.8 days), respectively.

We observed good tolerability of dupilumab during the study period, reporting AEs in 20.1%, consistently less than that observed in clinical trials (72.0%[14] and 60.0%[15]), and none of our patients discontinued dupilumab due to AEs. Conjunctivitis was confirmed to be the most frequent AE (10.9%), always being of mild-to-moderate severity and mostly worsening of pre-existent or reappearance of anamnestic conjunctivitis, both successfully treated with topical approaches. Prevalence of conjunctivitis observed in our study was in line with clinical trials (9.8%[14] and 16.0%[15]), while other AEs were less frequent: injection-site reaction (2.9% *vs* 9.8%[14] and 16.0%[15]), diarrhoea (1.4% *vs* 21.0%[15]), headache (0.7% *vs* 11.0%[14] and 26.0%[15]) and herpes simplex (0.7% *vs* 1.2%[14] and 11.0%[15]). We underline that dupilumab resulted safe in the 3 patients with asymptomatic SARS-CoV-2 infection, even if dupilumab was discontinued in 1 of them because of parents' concern. At the beginning of pandemic era, clinicians were in doubt whether to continue or discontinue dupilumab.[33] The results of the AD COVID-19 registries[34,35] and population-based cohort studies[36,37] demonstrate that dupilumab should be continued also in the pandemic as Th2 targeting with dupilumab do not increase the risk of SARS-CoV-2 infection or COVID-19 complications.

In conclusion, the strength of this real-world study is the large number of AD adolescents treated with dupilumab, not selected as in clinical trials. Limitations of this study include that part of patients (28.1%) had concomitant systemic therapy during the first 3–4 weeks that could influence baseline disease severity, effectiveness and safety of dupilumab. Another limitation is the short follow-up period and longer-term observational studies are needed to confirm effectiveness and safety of dupilumab in adolescent AD patients.

Data availability statement

Data available on request from the authors.

Acknowledgement

Open Access Funding provided by Universita degli Studi di Perugia within the CRUI-CARE Agreement.

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Appendix

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