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Short-, mid- and long-term efficacy of dupilumab in moderate-to-severe atopic dermatitis: a real-world multicentre Italian study of 2576 patients

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Abstract

Background The efficacy and safety of dupilumab in atopic dermatitis (AD) have been defined in clinical trials but limited real-world evidence on long-term treatment outcomes is currently available to inform clinical decisions.

Objectives To describe the long-term effectiveness and safety of dupilumab up to 48 months in patients with moderate-to-severe AD.

Methods A multicentre, retrospective, dynamic cohort study was conducted to assess long-term effectiveness and safety of dupilumab in patients with moderate-to-severe AD in a real-world setting. Predictors of minimal disease activity (MDA) optimal treatment target criteria [defined as the simultaneous achievement of a 90% reduction in Eczema Area and Severity Index score, itch-numeric rating scale (NRS) score ≤ 1, sleep-NRS score ≤ 1 and Dermatology Life Quality Index ≤ 1] were investigated.

Results In total, 2576 patients were enrolled from June 2018 to July 2022. MDA optimal treatment target criteria were achieved by 506/2309 (21.9%), 769/1959 (39.3%), 628/1247 (50.4%), 330/596 (55.4%) and 58/106 (54.7%) of those that reached 4, 12, 24, 36 and 48 months of follow-up, respectively. Logistic regression revealed a negative effect on MDA achievement for conjunctivitis and food allergy at all time-points. Adverse events (AEs) were mild and were observed in 373/2364 (15.8%), 166/2066 (8.0%), 83/1291 (6.4%), 27/601 (4.5%) and 5/110 (4.5%) of those that reached 4, 12, 24, 36 and 48 months of follow-up. Conjunctivitis was the most frequently reported AE during the available follow-up. AEs led to treatment discontinuation in < 1% of patients during the evaluated time periods.

Conclusions The high long-term effectiveness and safety of dupilumab were confirmed in this dynamic cohort of patients with moderate-to-severe AD, regardless of clinical phenotype and course (persisting or relapsing) at baseline. Further research will be needed to investigate the effect of T helper cell 2 comorbidities and disease duration on the response to dupilumab and other newer therapeutics for AD.

What is already known about this topic?

- The efficacy and safety of dupilumab in atopic dermatitis (AD) have been demonstrated in clinical trials but limited real-world evidence on long-term treatment outcomes is currently available to inform clinical decisions.

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What does this study add?

- High long-term effectiveness and safety of dupilumab were confirmed in this dynamic cohort of patients with moderate-to-severe AD, regardless of clinical phenotype and course at baseline.
- While certain AD phenotypes and a persisting AD course had a negative effect on the achievement of minimal disease activity at earlier timepoints, only conjunctivitis and food allergy retained significance as negative predictors at all timepoints.

Atopic dermatitis (AD) is a common, chronic-relapsing pruritic inflammatory cutaneous disorder with a negative impact on patients' quality of life (QoL) that often requires continuous long-term treatment for stable disease control.[1] Its prevalence in adulthood is increasing and in Italy is currently estimated at 8.1%.[2] The management and prevention of AD flares entails continued treatment; however, the prolonged use of conventional systemic immunosuppressive/immunomodulating agents (i.e. ciclosporin) is plagued by lack or loss of effectiveness and safety concerns.[3–5] Dupilumab, a monoclonal antibody that targets the alpha subunit of the interleukin (IL)-4 receptor,[6] thereby blocking IL-4/-13 signalling, has led to unprecedented objective and subjective improvements during its AD phase III studies. As a result of rapid and sustained efficacy as well as an optimal safety profile,[7–11] it has now been approved for the treatment of moderate-to-severe AD in both adults and adolescents/children in most countries.[12] Available analyses have confirmed dupilumab safety and sustained efficacy up to 52 weeks in a placebo-controlled study (LIBERTY AD CHRONOS) and up to 3 years in an open-label extension study (LIBERTY AD OLE) in adults with moderate-to-severe AD.[7,13,14]

Real-world evidence on long-term dupilumab use is still very limited but may be of critical importance in guiding patient management, especially now that multiple biologics and small molecules are available for the treatment of AD. Moreover, although patient-reported outcomes (PROs) have become crucial in capturing drug efficacy, most published studies have focused mainly on objective outcome measures. Recently, to overcome this, Silverberg *et al.* introduced the concept of minimal disease activity (MDA), combining both clinician-reported outcomes and PROs, to provide a practical but wholistic perspective on AD disease control.[15]

This real-world, retrospective multicentre nationwide dynamic cohort study aimed to describe the long-term effectiveness and safety of dupilumab up to 48 months in patients with moderate-to-severe AD. Achievement of MDA optimal treatment target criteria was analysed and possible predictors were investigated throughout the available follow-up.

Patients and methods

Data were retrospectively collected from patients with moderate-to-severe AD treated with dupilumab as standard care at 24 Italian dermatological centres from June 2018 to July 2022. Signed informed consent was obtained from patients in order to extract data from their clinical records. Approval of this study was obtained by the Local Ethics Committee—Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano (1157_2022).

Dupilumab was prescribed according to the recommendations of the Italian Drug Agency (AIFA).[16] As a real-world study, patients were allowed to use rescue medications (including topical corticosteroids or topical calcineurin inhibitors) as prescribed by their treating physicians once or twice a day for AD control in critical areas.

The following characteristics were collected at baseline: age at onset (adult onset is ≥ 18 years), disease duration (years), family history of AD, previous use of systemic therapies (antihistamines, corticosteroids, ciclosporin, phototherapy, methotrexate), presence of type 2 inflammatory comorbidities (asthma, rhinitis, conjunctivitis, nasal polyposis, eosinophilic oesophagitis, food allergy, urticaria), course (persisting or relapsing) and AD phenotype (classic with involvement of flexural areas and dryness; portrait phenotype; hand involvement; erythroderma; nummular-eczema-like; prurigo-like).

For objective and subjective evaluation, Eczema Area and Severity Index (EASI) scores and PROs, including weekly average numeric rating scale (NRS, range 0–10) for pruritus and sleep disturbances as well as Dermatology Life Quality Index (DLQI, range 0–30), recorded at the baseline and at 4, 12, 24, 36 and 48 months of follow-up, were extracted. Relative changes from the baseline were assessed at each timepoint and the rate of achievement of 75% (EASI 75), 90% (EASI 90) or 100% (EASI 100) improvements in EASI score was evaluated.

The achievement of MDA at each timepoint was also investigated. MDA optimal treatment target criteria were chosen as follows: EASI 90, itch-NRS score ≤ 1, sleep-NRS score ≤ 1 and DLQI ≤ 1. The achievement of MDA was defined as the simultaneous achievement of all the aforementioned clinician-reported outcomes and PROs. Predictors of MDA achievement at subsequent timepoints were also investigated.

The occurrence of adverse events (AEs) was assessed at each visit. Here, AEs were reported as occurring between the aforementioned timepoints. Importantly, all patients affected by conjunctivitis at baseline or developing conjunctivitis during follow-up were evaluated by an ophthalmologist and treated accordingly.

The primary endpoint was to identify predictors of MDA achievement at available timepoints. Secondary endpoints included achievement of EASI 75, EASI 90 and EASI 100, as well as PRO reductions at available timepoints.

Statistical analysis

Categorical variables are expressed as counts and percentages, whereas continuous variables are reported as medians and interquartile ranges (IQRs).

Univariate and multivariate logistic regression analyses were performed to assess the effect of the following features on the possibility of achieving MDA at 4, 12, 24 and 36 months: sex, age at enrolment, age at onset, AD duration,

presence of T helper cell (Th)2 comorbidities, AD course, predominant AD phenotype and previous treatments for AD.

Analyses at 48 months were not performed because of the limited sample size.

In order not to miss potential predictors, variables with $P < 0.1$ at univariate analysis were included in the multivariate models. A stepwise selection approach was then used to identify the best multivariate model, including only variables with statistically significant effects (P-values < 0.05, two sided). Estimated odds ratios (ORs), with their 95% confidence intervals (CIs), were obtained from logistic regression parameters.

All the statistical analyses were conducted with the statistical software SAS (release 9.4; SAS Institute, Inc., Cary, NC, USA).

Results

Effectiveness

In total, 2576 patients [median age 36 years (IQR 25–53); 54.6% (1407/2575) males] with moderate-to-severe AD were included, of whom 2364, 2066, 1291, 601 and 110 had data available for analysis at 4, 12, 24, 36 and 48 months, respectively. Detailed patient characteristics and trends for clinicians as well as PROs over time are shown in Table 1. Most patients had been previously treated with oral ciclosporin (1791/2576, 69.6%) or systemic corticosteroids (2245/2576, 87.3%).

The median EASI score at the baseline was 26 (IQR 24–30), decreasing to 3 (IQR 1–7), 1 (IQR 0–3), 1 (IQR 0–2), 0 (IQR 0–2) and 0.5 (IQR 0–1) for the subgroups that reached 4, 12, 24, 36 and 48 months, respectively. Proportions of EASI 75, EASI 90 and EASI 100 responders are shown in Figure 1.

Median DLQI decreased from 16 (IQR 11–20) at the baseline to 2 (IQR 1–5), 1 (IQR 0–3), 0 (IQR 0–2), 0 (IQR 0–2) and 0 (IQR 0–2) for the subgroups that reached 4, 12, 24, 36 and 48 months, respectively. Median Itch-NRS went from 9 (IQR 8–10) at the baseline to 2 (IQR 0–4), 1 (IQR 0–3), 1 (IQR 0–2), 1 (IQR 0–2) and 1 (IQR 0–2) in those that reached 4, 12, 24, 36 and 48 months, respectively. Median sleep-NRS decreased from 8 (IQR 6–10) to 0 (IQR 0–2), 0 (IQR 0–1), 0 (IQR 0–0), 0 (IQR 0–0) and 0 (IQR 0–0) at 4, 12, 24, 36 and 48 months, respectively.

MDA optimal treatment target criteria were achieved by 506 (21.9%, total $N = 2309$), 769 (39.2%, total $N = 1959$), 628 (50.4%, total $N = 1247$), 330 (55.4%, total $N = 596$) and 58 (54.7%, total $N = 106$) of those that reached 4, 12, 24, 36 and 48 months of follow-up, respectively.

Predictors of response in terms of MDA achievement in the univariate and multivariate analyses are detailed in Tables 2–5.

Safety

Overall, 373 (15.8%, total $N = 2364$), 166 (8.0%, total $N = 2066$), 83 (6.4%, total $N = 1291$), 27 (4.5%, total $N = 601$) and 5 (4.5%, total $N = 110$) of those that reached 4, 12, 24, 36 and 48 months of follow-up reported the occurrence of AEs, all mild in severity.

Conjunctivitis occurred in 216 (9.1%, total $N = 2364$) at 4 months, involving 95 (4.6%, total $N = 2066$), 45 (3.5%, total $N = 1291$), 19 (3.2%, total $N = 601$) and 4 (3.6%, total $N = 110$) at 12, 24, 36 and 48 months.

Facial redness was the second most reported AE at 4 months, occurring in 60 (2.5%, total $N = 2364$) patients and was recorded in 4 (0.2%, total $N = 2066$), 2 (0.2%, total $N = 1291$), 1 (0.2%, total $N = 601$) and 0 (0.0%, total $N = 110$) of those that reached 12, 24, 36 and 48 months of follow-up.

AE of interest, such as arthralgia and psoriasis, occurred in 10 (0.4%, total $N = 2364$) and 6 (0.3%, total $N = 2364$) at 4 months, with markedly lower figures at subsequent timepoints (Table 6).

Discontinuation of therapy

Details of withdrawals from therapy are reported in Table 7. Between enrolment and the 4-month visit, the first cause of discontinuation was loss to follow-up (55/2576, 2.1%). There were 29 (1.2%, total $N = 2364$), 16 (0.8%, total $N = 2066$), 6 (0.5%, total $N = 1291$) and 4 (0.7%, total $N = 601$) lost to follow-up between 5–12, 13–24, 25–36 and 37–48 months, respectively.

Discontinuation owing to AEs occurred in 13 (0.5%, total $N = 2576$), 18 (0.8%, total $N = 2364$), 13 (0.6%, total $N = 2066$), 7 (0.5%, total $N = 1291$) and 2 (0.3%, total $N = 601$) between 0–4, 5–12, 13–24, 25–36 and 37–48 months.

Discussion

In this real-world retrospective study, data on the long-term effectiveness and safety of dupilumab in patients with moderate-to-severe AD are presented. Objective and subjective outcome measures rapidly improved in the first 4 months and further ameliorated throughout the available follow-up. Overall, dupilumab was well tolerated with mild side-effects that led to interruption of therapy only in a minority of patients.

Based on EASI, itch-NRS and DLQI dupilumab showed similar results compared with those reported in previous phase III and real-world studies.[7–14,17,18] In a recently published paper by Beck *et al.*,[18] the authors evaluated the efficacy and safety of dupilumab over a period of 4 years in patients enrolled in the open-label extension study LIBERTY AD OLE. Among 2677 patients, an EASI 75 response was reached in 88.8% at 1 year and in 90.9% at 4 years. Our results were slightly better with an EASI 75 response obtained in 91.1% (1882/2066) after 1 year and in 98.2% (108/110) after 4 years. Ariens *et al.*[19] published a prospective observational study on the efficacy and safety of dupilumab in the long term (52 weeks), including 210 patients treated with dupilumab in daily practice. They reported an EASI 75 response in 70% of patients after 1 year. Such a difference compared with our results is remarkable considering the higher median EASI score (26, IQR 24–30) at baseline in our study compared with that reported by Ariens *et al.*,[19] and could be because of other baseline characteristics such as the previous use of immunosuppressant agents, which was more frequent in Ariens *et al.*[19]

The long-term effectiveness of dupilumab was also demonstrated through the PROs (DLQI, itch-NRS and sleep-NRS), whose trends were in line with other reported studies and real-world experiences.[18,20–23] In Ariens *et al.*, a median

Table 1 Demographics and clinical characteristics of included patients with atopic dermatitis (AD) at baseline and subsequent timepoints[a]

Characteristics	Baseline (*n*=2576)	4 months (*n*=2364)	12 months (*n*=2066)	24 months (*n*=1291)	36 months (*n*=601)	48 months (*n*=110)
Sex						
Male	1407/2575 (54.6)	1287/2362 (54.5)	1119/2064 (54.2)	700/1288 (54.4)	333/599 (56.6)	55/110 (50)
Female	1168/2575 (45.4)	1075/2362 (45.5)	945/2064 (45.8)	588/1288 (45.7)	266/599 (44.4)	55/110 (50)
Age (years), median (IQR)	36 (25–53)	36 (25–53)	36 (25–53)	37 (25–53)	40 (26–54)	42 (25–54)
Age (years) at onset, median (IQR)	3 (1–22)	3 (1–21)	3 (1–22)	3 (1–23)	3 (1–26)	3 (1–35)
AD duration (years), median (IQR)	22 (14–32)	22 (14–32)	22 (14–32)	23 (14–33)	23 (14–35)	22 (10–34)
Family history of AD	603/2576 (23.4)	573/2363 (24.2)	530/2065 (25.7)	352/1289 (27.3)	174/600 (29.0)	37/110 (33.6)
Family history of mucosal atopy	268/2575 (10.4)	263/2362 (11.1)	252/2064 (12.2)	157/1288 (12.2)	55/599 (9.2)	5/110 (4.5)
Th2 comorbidities						
Asthma	711/2423 (29.3)	674/2224 (30.3)	606/1940 (31.2)	392/1198 (32.7)	195/540 (36.1)	43/94 (45.7)
Rhinitis	1055/2423 (43.5)	970/2224 (43.6)	877/1940 (45.2)	580/1198 (48.4)	270/540 (50.0)	56/94 (59.6)
Conjunctivitis	711/2423 (29.3)	664/2224 (29.9)	601/1940 (31.0)	408/1198 (34.1)	201/540 (37.2)	42/94 (44.7)
Nasal polyposis	29/2423 (1.2)	24/2224 (1.1)	22/1940 (1.1)	18/1198 (1.5)	8/540 (1.5)	0/94 (0)
Eosinophilic oesophagitis	24/2423 (1.0)	24/2224 (1.1)	24/1940 (1.2)	16/1198 (1.3)	8/540 (1.5)	1/94 (1.1)
Food allergy	209/2423 (8.6)	192/2224 (8.6)	169/1940 (8.7)	114/1198 (9.5)	61/540 (11.3)	22/94 (23.4)
Urticaria	25/2423 (1.0)	23/2224 (1.0)	19/1940 (1.0)	12/1198 (1.0)	5/540 (0.9)	3/94 (3.2)
Non-Th2 comorbidities						
Diabetes	63/2184 (2.9)	59/2012 (2.9)	53/1752 (3.0)	40/1078 (3.7)	18/482 (3.7)	2/66 (3.0)
Coeliac disease	40/2184 (1.8)	40/2012 (2.0)	38/1752 (2.2)	29/1078 (2.7)	16/482 (3.3)	3/66 (4.5)
Alopecia areata	36/2184 (1.6)	36/2012 (1.8)	34/1752 (1.9)	29/1078 (2.7)	20/482 (4.1)	1/66 (1.5)
Autoimmune thyroiditis	51/2184 (2.3)	48/2012 (2.4)	41/1752 (2.3)	21/1078 (1.9)	11/482 (2.3)	2/66 (3.0)
Inflammatory bowel disease	10/2184 (0.5)	10/2012 (0.5)	8/1752 (0.5)	4/1078 (0.4)	2/482 (0.4)	0/66 (0)
Other	628/2184 (28.8)	578/2012 (28.7)	514/1752 (29.3)	328/1078 (30.4)	176/482 (36.5)	30/66 (45.5)
AD course						
Persisting	977/2382 (41.0)	899/2172 (41.4)	827/1878 (44.0)	569/1199 (47.5)	270/559 (48.3)	50/110 (45.5)
Relapsing	1405/2382 (59.0)	1273/2172 (58.6)	1051/1878 (56.0)	630/1199 (52.5)	289/559 (51.7)	60/110 (54.5)
Predominant AD phenotype						
Classic involvement of flexural areas and dryness	1872/2548 (73.5)	1713/2341 (73.2)	1486/2052 (72.4)	928/1276 (72.7)	433/597 (72.5)	76/110 (69.1)
Portrait	108/2548 (4.2)	108/2341 (4.6)	99/2052 (4.8)	67/1276 (5.3)	39/597 (6.5)	11/110 (10.0)
Hand involvement	169/2548 (6.6)	165/2341 (7.1)	161/2052 (7.8)	77/1276 (6.0)	20/597 (3.4)	2/110 (1.8)
Erythrodermic	78/2548 (3.1)	69/2341 (3.0)	54/2052 (2.6)	39/1276 (3.1)	16/597 (2.7)	4/110 (3.6)
Nummular-eczema-like	100/2548 (3.9)	90/2341 (3.8)	77/2052 (3.8)	48/1276 (3.8)	32/597 (5.4)	6/110 (5.5)
Prurigo-like	221/2548 (8.7)	196/2341 (8.4)	175/2052 (8.5)	117/1276 (9.2)	57/597 (9.5)	11/110 (10.0)
Previous systemic therapy for AD						
Antihistamines	1814/2572 (70.5)	1665/2360 (70.6)	1426/2062 (69.2)	890/1287 (69.2)	401/598 (67.1)	72/110 (65.5)
Corticosteroids	2245/2572 (87.3)	2067/2360 (87.6)	1800/2062 (87.3)	1120/1287 (87.0)	528/598 (88.3)	102/110 (92.7)
Ciclosporin A	1791/2572 (69.6)	1655/2360 (70.1)	1444/2062 (70.0)	931/1287 (72.3)	423/598 (70.7)	72/110 (65.5)
Phototherapy	548/2572 (21.3)	512/2360 (21.7)	467/2062 (22.6)	301/1287 (23.4)	143/598 (23.9)	32/110 (29.1)
Methotrexate	76/2572 (3.0)	68/2360 (2.9)	61/2062 (3.0)	44/1287 (3.4)	24/598 (4.0)	7/110 (6.4)
EASI, median (IQR)	26 (24–30)	3 (1–7)	1 (0–3)	1 (0–2)	0 (0–2)	0.5 (0–1)
Median % EASI reduction (IQR)	–	89 (76–97)	96 (88–100)	97 (92–100)	100 (93–100)	99 (96–100)
EASI ≤ 7	20/2567 (0.8)	1808/2364 (76.5)	1923/2066 (93.1)	1249/1291 (96.8)	586/601 (97.5)	108/110 (98.2)
DLQI, median (IQR)	16 (11–20)	2 (1–5)	1 (0–3)	0 (0–2)	0 (0–2)	0 (0–2)
DLQI ≤ 10	620/2561 (24.2)	2166/2354 (92.0)	1993/2058 (96.8)	1269/1289 (98.4)	590/600 (98.3)	106/109 (97.3)
DLQI ≤ 1	15/2561 (0.60)	855/2354 (36.3)	1181/2058 (57.4)	842/1289 (65.3)	412/600 (68.7)	73/109 (67.0)
Itch-NRS, median (IQR)	9 (8–10)	2 (0–4)	1 (0–3)	1 (0–2)	1 (0–2)	1 (0–2)
Itch-NRS ≤ 6	155/2565 (6.0)	2123/2363 (89.8)	1932/2054 (94.1)	1231/1291 (95.4)	578/600 (96.3)	107/110 (97.3)
Itch-NRS ≤ 1	5/2565 (0.2)	969/2363 (41.0)	1102/2054 (53.7)	785/1291 (60.8)	392/600 (65.3)	76/110 (69.1)
Sleep-NRS, median (IQR)	8 (6–10)	0 (0–2)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)
Sleep-NRS ≤ 6	740/2551 (29.0)	2172/2318 (93.7)	1917/1968 (97.4)	1226/1247 (98.3)	588/596 (98.7)	106/107 (99.1)
Sleep-NRS ≤ 1	165/2551 (6.5)	1524/2318 (65.8)	1575/1968 (80.0)	1064/1247 (85.3)	507/596 (85.1)	102/107 (95.3)
EASI 75	–	1754/2364 (74.2)	1882/2066 (91.1)	1232/1291 (95.4)	582/601 (96.8)	108/110 (98.2)
EASI 90	–	1142/2364 (48.3)	1468/2066 (71.1)	1056/1291 (81.8)	523/601 (87.0)	94/110 (85.5)
EASI 100	–	516/2364 (21.8)	759/2066 (36.7)	613/1291 (47.5)	333/601 (55.4)	55/110 (50.0)
MDA	–	506/2309 (21.9)	769/1959 (39.3)	628/1247 (50.4)	330/596 (55.4)	58/106 (54.7)

Data are *n/N* (%) unless otherwise specified. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IQR, interquartile range; MDA, minimal disease activity; NRS, numerical rating scale; Th2, T helper cell 2. [a]At each timepoint, for each variable some data were missing, relative to the total reported in the first row.

DLQI score of 3 after 1 year of treatment was recorded,[19] whereas in our study the median DLQI score (1, IQR 0–3) was slightly lower at the same timepoint.

Beck *et al.* reported a mean itch-NRS of 2.37 at 1 year and of 2.10 at 4 years of treatment.[18] In our study, better results were obtained with a median itch-NRS of 1 (IQR 0–3) after 1 year and of 1 (IQR 0–2) after 4 years. Although also allowed in Beck *et al.*, use of rescue medications in relation to the status of the patients in our study may have contributed to this discrepancy.[18]

Several clinical and immunological phenotypes of AD have been described,[24] with possible nuances in terms of treatment response. Involvement of sensitive areas (i.e. head, neck, hands and genitalia), which overlap only in part

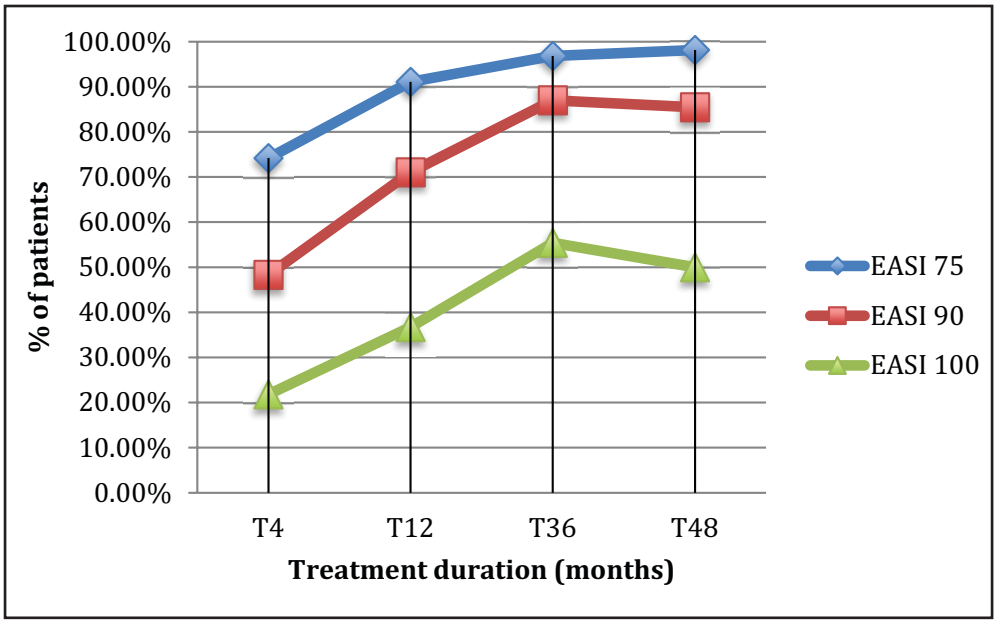

Figure 1 Percentage of patients reaching the rate of achievement of 75% [Eczema Area and Severity Index (EASI) 75], 90% (EASI 90) and 100% (EASI 100) improvements at the different timepoints. T4, 4 months; T12, 12 months; T36, 36 months; T48, 48 months.

with the described phenotypes, also merits adequate consideration, as it has an impact on QoL and response to treatment.[25,26] In the present study, predictors of achievement of MDA optimal treatment target criteria were investigated. At univariate regression, in the short term (4 months), patients with hand involvement, erythrodermic, nummular-eczema-like and prurigo-like phenotypes had lower odds of achieving the established optimal treatment target compared with those with classic AD. At 12 months, differences in terms of MDA achievement relative to classic AD were lost for erythrodermic and nummular-eczema-like forms but persisted for the prurigo-like phenotype. This negative effect was lost later on.

Similarly, history of persisting (as compared with relapsing) AD was a negative predictor of MDA achievement at 4 and 12 months, but not at subsequent timepoints. Conversely, those with hand involvement and portrait AD had higher odds of reaching the optimal treatment target, retaining statistical significance at 24 and, for hand involvement, 36 months. Multivariate logistic regression confirmed the initial negative effect on MDA achievement of certain AD phenotypes (erythrodermic, nummular-eczema-like, prurigo-like) and of persistent AD course, but this was limited to the first 12 and 24 months, respectively. Indeed, according to a study by Tavecchio *et al.*, patients with prurigo-like and nummular-eczema-like AD phenotypes tend to be late responders to the drug but reach EASI 75 at 1 year, similar to people with the other forms.[27] Conversely, higher odds of achieving MDA optimal treatment target criteria in those with hand involvement are in line with recent evidence of efficacy of dupilumab in chronic hand eczema.[26]

Disease duration seemed not to influence MDA achievement at earlier timepoints, but AD duration of ≥5 years predicted lower odds of achieving MDA optimal treatment target criteria at 36 months of treatment in univariate analysis. Although available evidence indicates that dupilumab may prevent the progression of the atopic march,[28] no studies have investigated the effect of early treatment on AD response, as has been extensively assessed in psoriasis.[29]

Of other potential predictors, early onset (i.e. before 18 years of age) of AD, age at enrolment < 18 years and presence of atopic comorbidities, particularly conjunctivitis, rhinitis and food allergy, negatively influenced MDA achievement in the long-term in the univariate regression. However, only conjunctivitis and food allergy retained significance as negative predictors at all timepoints in the multivariate analysis.

Concerning dupilumab safety, reported AEs were all mild in severity. Their incidence was low and tended to reduce during follow-up, from 8.0% (166/2066) in the first, to 6.4% (83/1291) in the second, 4.5% (27/601) in the third and 4.5% (5/110) in the fourth year. This is in line with the authors' experience, with the majority of AEs occurring at treatment initiation.

The reported incidence of conjunctivitis in clinical trials.[6,7,9,13,30] and in real-world studies[19,20] ranges, respectively, from 5% to 28% and from 6% to 62%. In the present study, the incidence of conjunctivitis was 9.1% (216/2364) at 4 months of therapy, decreasing over time to 3.6% (4/110) at 48 months. This finding may be because of the use of preventive and rescue medication for this aspect in Italy.[31] Indeed, prompt ophthalmological referral and follow-up management are key in preventing or ameliorating conjunctivitis, possibly avoiding drug discontinuation as a consequence of this AE.

The number of individuals discontinuing treatment was low and in line with previous studies.[14,18,19]

The strengths of this study include the duration of treatment and follow-up as well as the large sample size. Limitations include its retrospective nature and dynamic cohort design that hindered considerations regarding drug survival. There may be differences in patient characteristics between trials and daily practice, hampering direct comparison; however, this real-world study showed remarkable

Table 2 Odds ratios (OR) and 95% confidence intervals (CIs) for minimal disease activity (MDA) achievement at 4 months in univariate and multivariate regression analyses[a]

	Univariate		Multivariate	
MDA at 4 months	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)		**0.07**	NS	NS
18–64	1[b]			
< 18	0.466 (0.239–0.909)			
≥ 65	0.911 (0.665–1.249)			
Sex		0.86		–
Male	1[b]		–	
Female	0.982 (0.806–1.197)		–	
Age at onset (years)		0.97		–
≥ 18	1[b]		–	
< 18	0.995 (0.802–1.235)		–	
AD duration (years)		0.12		–
< 5	1[b]		–	
≥ 5	1.328 (0.929–1.898)		–	
Th2 comorbidities				
Asthma		**< 0.001**	NS	NS
No	1[b]			
Yes	0.658 (0.522–0.829)			
Rhinitis		**< 0.001**		**< 0.001**
No	1[b]		1[b]	
Yes	0.445 (0.358–0.553)		0.575 (0.435–0.761)	
Conjunctivitis		**< 0.001**		**0.02**
No	1[b]		1[b]	
Yes	0.482 (0.376–0.616)		0.674 (0.489–0.929)	
Nasal polyposis		0.99		–
No	1[b]		–	
Yes	1.009 (0.370–2.749)		–	
Eosinophilic oesophagitis		0.62		–
No	1[b]		–	
Yes	0.761 (0.256–2.258)		–	
Food allergy		**<0.001**	NS	NS
No	1[b]			
Yes	0.359 (0.221–0.583)			
Urticaria		0.37		–
No	1[b]		–	
Yes	1.509 (0.617–3.688)		–	
AD course		**<0.001**		**< 0.001**
Relapsing	1[b]		1[b]	
Persisting	0.517 (0.413–0.646)		0.550 (0.429–0.705)	
Predominant AD phenotype		**<0.001**		**< 0.001**
Classic	1[b]		1[b]	
Portrait	1.103 (0.707–1.722)		1.015 (0.631–1.633)	
Hand involvement	**0.530 (0.339–0.828)**		**0.508 (0.319–0.809)**	
Erythrodermic	**0.317 (0.136–0.739)**		**0.317 (0.133–0.757)**	
Nummular-eczema-like	**0.222 (0.096–0.513)**		**0.222 (0.095–0.519)**	
Prurigo-like	**0.599 (0.399–0.899)**		**0.472 (0.298–0.748)**	
Previous therapy for AD				
Antihistamines		**0.09**		**0.001**
No	1[b]		1[b]	
Yes	0.834 (0.675–1.032)		0.626 (0.474–0.827)	
Systemic corticosteroids		0.96		–
No	1[b]		–	
Yes	1.008 (0.746–1.362)		–	
Ciclosporin		0.25		–
No	1[b]		–	
Yes	1.136 (0.913–1.415)		–	
Phototherapy		**< 0.001**	NS	NS
No	1[b]			
Yes	0.620 (0.477–0.805)			
Methotrexate		0.49		–
No	1[b]		–	
Yes	0.800 (0.424–1.509)		–	

AD, atopic dermatitis; Th2, T helper cell 2. [a]Variables with $P < 0.1$ at univariate analysis were included in multivariate analysis. The best multivariate model (far right column), including only variables with statistically significant (P values < 0.05) effects, was then identified through a stepwise selection approach. Results with $P < 0.1$ at univariate and $P < 0.05$ at multivariate analysis are reported in bold. '–', $P > 0.1$ at univariate analysis and thus not included in multivariate analysis; NS, variables with $P < 0.1$ at univariate analyses that were not significant in multivariate analysis, were discarded via a stepwise selection approach and thus were not included in the final model. [b]Reference category.

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) for minimal disease activity (MDA) achievement at 12 months in univariate and multivariate regression analyses[a]

	Univariate		Multivariate	
MDA at 12 months	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)		**0.004**	NS	NS
18–64	1[b]			
< 18	0.452 (0.267–0.766)			
≥ 65	0.767 (0.569–1.034)			
Sex		0.54		–
Male	1[b]		–	
Female	1.058 (0.882–1.267)		–	
Age at onset (years)		0.73		–
≥ 18	1[b]		–	
< 18	1.036 (0.850–1.262)		–	
AD duration (years)		0.85		–
< 5	1[b]		–	
≥ 5	0.970 (0.714–1.318)		–	
Th2 comorbidities				
Asthma		**< 0.001**		**0.002**
No	1[b]		1[b]	
Yes	0.571 (0.465–0.701)		0.688 (0.543–0.873)	
Rhinitis		**0.03**	NS	NS
No	1[b]			
Yes	0.817 (0.678–0.984)			
Conjunctivitis		**< 0.001**		**0.002**
No	1[b]		1[b]	
Yes	0.603 (0.491–0.740)		0.684 (0.539–0.867)	
Nasal polyposis		0.90		–
No	1[b]		–	
Yes	0.949 (0.404–2.231)		–	
Eosinophilic oesophagitis		0.77		–
No	1[b]		–	
Yes	0.881 (0.380–2.047)		–	
Food allergy		**< 0.001**		**<0.001**
No	1[b]		1[b]	
Yes	0.197 (0.125–0.309)		0.222 (0.138–0.357)	
Urticaria		0.17		–
No	1[b]		–	
Yes	0.487 (0.175–1.357)		–	
AD course		**< 0.001**		**< 0.001**
Relapsing	1[b]		1[b]	
Persisting	0.535 (0.440–0.649)		0.591 (0.474–0.736)	
Predominant AD phenotype		**< 0.001**		**< 0.001**
Classic	1[b]		1[b]	
Portrait	**1.720 (1.136–2.603)**		**1.720 (1.136–2.603)**	
Hand involvement	**6.299 (4.230–9.379)**		**6.299 (4.230–9.379)**	
Erythrodermic	0.660 (0.352–1.238)		0.660 (0.352–1.238)	
Nummular-eczema-like	0.792 (0.481–1.304)		0.792 (0.481–1.304)	
Prurigo-like	**0.646 (0.450–0.926)**		**0.646 (0.450–0.926)**	
Previous therapy for AD				
Antihistamines		**0.004**		**< 0.001**
No	1[b]		1[b]	
Yes	1.339 (1.099–1.632)		0.623 (0.475–0.816)	
Systemic corticosteroids		0.39		–
No	1[b]		–	
Yes	0.887 (0.674–1.167)		–	
Ciclosporin		**0.07**	NS	NS
No	1[b]			
Yes	1.203 (0.985–1.469)			
Phototherapy		0.15		–
No	1[b]		–	
Yes	1.168 (0.943–1.446)		–	
Methotrexate		0.83		–
No	1[b]		–	
Yes	1.061 (0.622–1.809)		–	

AD, atopic dermatitis; Th2, T helper cell 2. [a]Variables with $P<0.1$ at univariate analysis were included in multivariate analysis. The best multivariate model (far right column), including only variables with statistically significant (P values <0.05) effects, was then identified through a stepwise selection approach. Results with $P<0.1$ at univariate and $P<0.05$ at multivariate analysis are reported in bold. '–', $P>0.1$ at univariate analysis and thus not included in multivariate analysis; NS, variables with $P<0.1$ at univariate analyses that were not significant in multivariate analysis, were discarded via a stepwise selection approach and thus were not included in the final model. [b]Reference category.

Table 4 Odds ratios (ORs) and 95% confidence intervals (CIs) for minimal disease activity (MDA) achievement at 24 months in univariate and multivariate regression analyses[a]

	Univariate		Multivariate	
MDA at 24 months	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)				
18–64	1[b]	0.44	–	–
< 18	0.756 (0.390–1.465)		–	
≥ 65	1.185 (0.828–1.695)		–	
Sex				–
Male	1[b]	0.67	–	
Female	0.952 (0.762–1.190)		–	
Age at onset (years)		0.29		–
≥ 18	1[b]		–	
< 18	0.876 (0.686–1.119)		–	
AD duration (years)		0.95		–
< 5	1[b]		–	
≥ 5	1.013 (0.697–1.472)		–	
Th2 comorbidities				
Asthma		0.38		–
No	1[b]		–	
Yes	0.896 (0.701–1.144)		–	
Rhinitis		0.34		–
No	1[b]		–	
Yes	0.893 (0.709–1.125)		–	
Conjunctivitis		**< 0.001**		**< 0.001**
No	1[b]		1[b]	
Yes	0.616 (0.483–0.787)		0.633 (0.482–0.831)	
Nasal polyposis		0.11		–
No	1[b]		–	
Yes	2.345 (0.831–6.621)		–	
Eosinophilic oesophagitis		0.44		–
No	1[b]		–	
Yes	1.494 (0.540–4.139)		–	
Food allergy		**< 0.0001**		**< 0.001**
No	1[b]		1[b]	
Yes	0.446 (0.298–0.667)		0.445 (0.290–0.684)	
Urticaria		0.44		–
No	1[b]		–	
Yes	0.634 (0.200–2.009)		–	
AD course		**0.08**		**0.03**
Relapsing	1[b]		1[b]	
Persisting	0.815 (0.647–1.028)		0.749 (0.578–0.971)	
Predominant AD phenotype		**< 0.001**		**< 0.001**
Classic	1[b]		1[b]	
Portrait	2.007 (1.190–3.386)		**1.920 (1.096–3.363)**	
Hand involvement	3.519 (2.043–6.061)		**2.849 (1.632–4.973)**	
Erythrodermic	0.805 (0.407–1.593)		0.753 (0.360–1.575)	
Nummular-eczema-like	0.755 (0.414–1.378)		0.669 (0.342–1.307)	
Prurigo-like	0.923 (0.616–1.382)		0.799 (0.511–1.249)	
Previous therapy for AD				
Antihistamines		0.36		**< 0.001**
No	1[b]		1[b]	
Yes	1.119 (0.881–1.421)		0.577 (0.417–0.798)	
Systemic corticosteroids		**0.02**		**0.03**
No	1[b]		1[b]	
Yes	0.674 (0.482–0.944)		0.651 (0.437–0.968)	
Ciclosporin		**0.04**	NS	NS
No	1[b]			
Yes	0.771 (0.601–0.989)			
Phototherapy		0.46		–
No	1[b]		–	
Yes	0.906 (0.697–1.177)		–	
Methotrexate		0.20		–
No	1[b]		–	
Yes	0.668 (0.363–1.232)		–	

AD, atopic dermatitis; Th2, T helper cell 2. [a]Variables with $P < 0.1$ at univariate analysis were included in multivariate analysis. The best multivariate model (far right column), including only variables with statistically significant (P values < 0.05) effects, was then identified through a stepwise selection approach. Results with $P < 0.1$ at univariate and $P < 0.05$ at multivariate analysis are reported in bold. '–', $P > 0.1$ at univariate analysis and thus not included in multivariate analysis; NS, variables with $P < 0.1$ at univariate analyses that were not significant in multivariate analysis, were discarded via a stepwise selection approach and thus were not included in the final model. [b]Reference category.

Table 5 Odds ratios (ORs) and 95% confidence intervals (CIs) for minimal disease activity (MDA) achievement at 36 months in univariate and multivariate regression analyses

	Univariate		Multivariate	
MDA at 36 months	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)		**0.03**	NS	NS
18–64	1[b]			
< 18	0.245 (0.079–0.762)			
≥ 65	1.366 (0.776–2.403)			
Sex		0.84		–
Male	1[b]		–	
Female	0.967 (0.698–1.339)		–	
Age at onset (years)		**< 0.001**	NS	NS
≥ 18	1[b]			
< 18	0.485 (0.336–0.699)			
AD duration (years)		**0.04**	NS	NS
< 5	1[b]			
≥ 5	0.547 (0.309–0.967)			
Th2 comorbidities				
Asthma		0.15		–
No	1[b]		–	
Yes	0.770 (0.540–1.098)		–	
Rhinitis		**0.03**	NS	NS
No	1[b]			
Yes	0.680 (0.482–0.959)			
Conjunctivitis		**< 0.001**		**< 0.001**
No	1[b]		1[b]	
Yes	0.410 (0.286–0.586)		0.417 (0.284–0.614)	
Nasal polyposis		0.75		–
No	1[b]		–	
Yes	1.267 (0.300–5.355)		–	
Eosinophilic oesophagitis		0.75		–
No	1[b]		–	
Yes	0.414 (0.239–0.717)		–	
Food allergy		**0.002**		**0.02**
No	1[b]		1[b]	
Yes	0.414 (0.239–0.717)		0.489 (0.273–0.877)	
Urticaria		0.13		–
No	1[b]		–	
Yes	0.187 (0.021–1.681)		–	
AD course		0.18		–
Relapsing	1[b]		–	
Persisting	0.794 (0.568–1.112)		–	
Predominant AD phenotype		**0.02**	NS	NS
Classic	1[b]			
Portrait	1.934 (0.947–3.949)			
Hand involvement	**8.354 (1.915–36.446)**			
Erythrodermic	0.928 (0.342–2.518)			
Nummular-eczema-like	1.547 (0.738–3.243)			
Prurigo-like	1.477 (0.839–2.600)			
Previous therapy for AD				
Antihistamines		0.99		–
No	1[b]		–	
Yes	0.999 (0.707–1.411)		–	
Systemic corticosteroids		**0.03**		**0.03**
No	1[b]		1[b]	
Yes	0.550 (0.322–0.938)		0.504 (0.261–0.976)	
Ciclosporin		**0.05**	NS	NS
No	1[b]			
Yes	0.703 (0.490–1.007)			
Phototherapy		> 0.99		–
No	1[b]		–	
Yes	0.999 (0.684–1.461)		–	
Methotrexate		0.49		–
No	1[b]		–	
Yes	1.344 (0.579–3.122)		–	

AD, atopic dermatitis; Th2, T helper cell 2. [a]Variables with $P < 0.1$ at univariate analysis were included in multivariate analysis. The best multivariate model (far right column), including only variables with statistically significant (P values < 0.05) effects, was then identified through a stepwise selection approach. Results with $P < 0.1$ at univariate and $P < 0.05$ at multivariate analysis are reported in bold. '–', $P > 0.1$ at univariate analysis and thus not included in multivariate analysis; NS, variables with $P < 0.1$ at univariate analyses that were not significant in multivariate analysis, were discarded via a stepwise selection approach and thus were not included in the final model. [b]Reference category.

Table 6 Reported adverse events (AEs) during the follow-up period

AEs	4 months (*n*=2364)	12 months (*n*=2066)	24 months (*n*=1291)	36 months (*n*=601)	48 months (*n*=110)
Total participants who experienced AEs	373 (15.8)	166 (8.0)	83 (6.4)	27 (4.5)	5 (4.5)
Reaction to site injection	28 (1.2)	21 (1.0)	6 (0.5)	2 (0.3)	0 (0.0)
Conjunctivitis	216 (9.1)	95 (4.6)	45 (3.5)	19 (3.2)	4 (3.6)
Asthenia	8 (0.3)	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Headache	8 (0.3)	2 (0.1)	2 (0.2)	1 (0.2)	0 (0.0)
Arthralgia	10 (0.4)	6 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)
Psoriasis	6 (0.3)	4 (0.2)	2 (0.2)	1 (0.2)	0 (0.0)
Alopecia areata	1 (0.04)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Facial redness	60 (2.5)	4 (0.2)	2 (0.2)	1 (0.2)	0 (0.0)
Herpetic reactivation	18 (0.8)	15 (0.7)	13 (1.0)	2 (0.3)	1 (0.9)
Other	18 (0.8)	16 (0.8)	11 (0.9)	1 (0.2)	0 (0.0)

Data are *n* (%).

Table 7 Reasons for discontinuation during the follow-up period

Discontinuation[a]	0–4 months	5–12 months	13–24 months	25–36 months	37–48 months
Discontinuation for any reason	95 (3.7)	85 (3.6)	69 (3.3)	35 (2.7)	12 (2.0)
Owing to lack of effectiveness	4 (0.2)	17 (0.7)	17 (0.8)	6 (0.5)	3 (0.5)
Owing to AE	13 (0.5)	18 (0.8)	13 (0.6)	7 (0.5)	2 (0.3)
Owing to SARS-CoV-2 infection	5 (0.2)	3 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)
Owing to pregnancy	1 (0.04)	3 (0.1)	4 (0.2)	2 (0.2)	2 (0.3)
Owing to loss to follow-up	55 (2.1)	29 (1.2)	16 (0.8)	6 (0.5)	4 (0.7)
Owing to clinical remission	1 (0.04)	4 (0.2)	7 (0.3)	6 (0.5)	1 (0.2)
Owing to personal choice	7 (0.3)	8 (0.3)	8 (0.4)	4 (0.3)	0 (0.0)
Owing to other causes	9 (0.3)	4 (0.2)	6 (0.3)	4 (0.3)	0 (0.0)

Data are *n* (%). AE, adverse event. [a]Calculated based on the total of patients at risk for discontinuation at the beginning of each period, i.e. 2576, 2364, 2066, 1291 and 601, respectively.

effectiveness of dupilumab in AD up to 48 months, with outcomes rivalling and sometimes even surpassing those reported in published clinical trials.

Importantly, although some features may play a role in predicting the response to dupilumab (such as history of conjunctivitis or food allergies), the optimal treatment target, according to the MDA concept, was reached in the long term, regardless of AD clinical phenotype or course at baseline. Further research will be needed to investigate the effect of disease duration and Th2 comorbidities on the response to treatment in relation to forthcoming therapeutics for AD.

In conclusion, this large, multicentre, retrospective real-world study confirms the sustained effectiveness and optimal safety profile of dupilumab in moderate-to-severe AD, and in the long term. Incremental improvements in both subjective and objective outcome measures were observed, as well as a decreasing trend in the incidence of AE over time, corroborating data obtained in clinical trials.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement

Approval of this study was obtained by the Local Ethics Committee – Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milano (1157_2022).

Patient consent

All patients gave written, informed consent for participation and publication.

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