Use of Dupilumab for 543 Adult Patients with Moderate-To-Severe Atopic Dermatitis: A Multicenter, Retrospective Study

Short title: Use of Dupilumab: A Multicenter Study

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Abstract

Background: Dupilumab has been demonstrated to be an effective treatment for patients with moderate-to-severe atopic dermatitis (AD) in clinical trials. However, evidence of real-world experience with dupilumab in a broader population is limited to date.

Methods: Adult patients with moderate-to-severe AD, defined as an Eczema Area Severity Index (EASI) score of 24 or higher, treated with dupilumab at ten Italian academic centers, were included in the study. Physician-reported outcome measures (EASI), patient-reported outcome measures (pruritus and sleep score, Dermatology Life Quality Index, DLQI) and serological markers [immunoglobulin (Ig) E and eosinophil count] after 16 weeks were analyzed.

Results: We enrolled 543 patients with moderate-to-severe AD. Two patients (0.4%) discontinued treatment. The median ± interquartile percentage change from baseline to 16 weeks of treatment in the EASI score was -87.5±22.0 ($p<0.001$). EASI-50, EASI-75 and EASI-90 response rates were 98.1%, 81.5%, and 50.8% after 16 weeks. At 16 weeks, 93.0% of the patients had achieved a 4-point or higher improvement in DLQI from baseline.

During dupilumab treatment, 12.2% of the patients developed conjunctivitis, and total IgE significantly decreased ($p<0.001$). Interestingly, in the multivariate logistic regression model, the risk of developing dupilumab-related conjunctivitis was associated with early AD onset [OR, 2.25; 95%CI, 1.07–4.70; $p=0.03$] and presence of eosinophilia [OR, 1.91; 95%CI, 1.05–3.39; $p=0.03$].

Conclusion: To date, this is the broadest real-life study in AD patients treated with dupilumab. We observed significant improvements induced by dupilumab in adult patients with moderate-to-severe AD, to a greater extent than those reported in clinical trials.

Key words: Atopic dermatitis. Dupilumab. Multicentric real-life study.

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Resumen

Antecedentes: se ha demostrado en ensayos clínicos que dupilumab es un tratamiento eficaz para pacientes con dermatitis atópica (DA) de moderada a grave. Sin embargo, la experiencia en vida real con dupilumab y con gran número de pacientes es más limitada.

Métodos: Se incluyeron en el estudio pacientes adultos con DA de moderada a grave, definida como un índice de gravedad del área de eccema (EASI) de 24 o más, tratados con dupilumab en diez centros universitarios italianos. Se analizaron parámetros medidos por el médico (EASI), por el paciente (puntuación de prurito y sueño, índice de calidad de vida dermatológica, DLQI) y marcadores serológicos (inmunoglobulina IgE y recuento de eosinófilos en sangre) a las 16 semanas de tratamiento.

Resultados: Se incluyeron 543 pacientes con DA de moderada a grave. Dos pacientes (0,4%) interrumpieron el tratamiento. La mediana ± cambio porcentual intercuartílico desde el inicio hasta las 16 semanas de tratamiento en la puntuación EASI fue -87,5 ± 22,0 ($p < 0,001$). Las tasas de respuesta de EASI-50, EASI-75 y EASI-90 fueron del 98,1%, 81,5% y 50,8% después de 16 semanas. En la semana 16, el 93% de los pacientes habían logrado una mejora de 4 puntos o más en el DLQI desde el inicio.

Durante el tratamiento con dupilumab, el 12,2% de los pacientes desarrollaron conjuntivitis y la IgE total disminuyó significativamente ($p < 0,001$). Curiosamente, en el modelo de regresión logística multivariante, el riesgo de desarrollar conjuntivitis relacionada con dupilumab se asoció con la aparición temprana de DA (OR, 2,25; IC del 95%, 1.07–4.70; $p = 0,03$) y presencia de eosinofilia (OR, 1,91; IC del 95%, 1,05–3,39; $p = 0,03$).

Conclusión: Hasta la fecha, este es el estudio más amplio en vida real en pacientes con DA tratados con dupilumab. Se observaron mejoras significativas y más importantes que las notificadas en los ensayos clínicos realizados con dupilumab.

Palabras clave: Dermatitis atópica. Dupilumab. Estudio multicéntrico en vida real.

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Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease, with a prevalence of 2–8% in the adult population and up to 20% in infants in most countries around the world [1]. Affected patients suffer from persistent or relapsing skin lesions associated with a spectrum of atopic comorbidities [2]. AD negatively impacts the quality of life (QoL) of patients in health-related aspects such as physical, psychosocial, and mental functioning [3]. Key features of lesional skin from AD patients include skin barrier defects, impaired cornified envelope formation, and aberrant keratinocyte differentiation [4]. Increased expression of the T2 cytokine axis occurs in AD, in which interleukin (IL)-4 and IL-13 play a major role [5]. Topical emollients, corticosteroids and calcineurin inhibitors remain the mainstay of AD therapy, especially in mild cases [1,6]; however, moderate-to-severe AD often cannot be adequately controlled with topical treatments and requires the use of systemic agents [1,6,7]. Dupilumab, a fully human monoclonal IgG4 antibody, inhibits IL-4 and IL-13 signal transduction through competitively binding to the shared α subunit of the IL-4 receptor [8]. Blockade of IL-4/13 is effective in reducing the T helper (Th) 2 response.

Dupilumab is the first biologic agent to have been approved for the treatment of patients with inadequately controlled moderate-to-severe AD. Efficacy and safety of dupilumab have been investigated in three main placebo-controlled phase III trials: the identically-designed SOLO 1 and 2 studies [9], which examined the drug as monotherapy; and the CAFÉ [10] and CHRONOS [11] studies, which assessed the drug administered concomitantly with topical corticosteroids as background therapy. The first two trials [9,10] found a significant improvement in measures of skin clearing and overall severity of the disease at 16 weeks of treatment, and the third [11] found a significant improvement in overall disease severity at 16 and 52 weeks.

As limited data on dupilumab treatment are available in a daily practice setting, it is important to assess the performance of this treatment in real clinical practice and in a broader

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population. We studied 543 Italian adult patients with moderate-to-severe, difficult-to-treat AD treated with dupilumab, and herein we report our real-world data regarding dupilumab treatment.

Methods

Study design and participants

We performed a multicenter retrospective chart review including adult patients with moderate-to-severe AD who had started dupilumab treatment in the context of standard care from September 2018 to April 2020 at ten Italian academic allergological/dermatological centers. Dupilumab was prescribed according to the Italian Drug Agency (AIFA) recommendations. In order to participate in this study, each centre had to provide data on patients aged 18 years and older with moderate-to-severe AD, defined as an Eczema Area Severity Index (EASI) score of 24 or higher and who had inadequate response to/intolerance for Cyclosporin A (CsA), or who were medically classified as unsuitable for CsA treatment based on the criteria established by the AIFA for patient enrolment. Patients included in the study had failed to respond adequately to topical treatments.

All procedures complied with the Helsinki Declaration of 1964, revised in 2013.

The study protocol was approved by the Ethics Committee of Naples Federico II University Hospital, Italy. All patients received full information at the medical visit, and gave written consent for the investigators to extract relevant data from patient records.

A 600-mg loading dose of dupilumab was injected subcutaneously at baseline, followed by an injection of 300 mg dupilumab every other week.

A wash-out period was not required. Any topical approved AD treatments were permitted as needed or else a shared decision was made to use topical medications as needed during therapy with dupilumab. Patients receiving systemic treatments during dupilumab therapy were excluded from the study. Throughout the study period, patients were required to maintain their pre-treatment therapy for the management of atopic comorbidities.

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Patients were assessed for medical history, demographics, allergic comorbidities (i.e., allergic rhinoconjunctivitis, allergic asthma and food allergies), concomitant medications or procedures, adverse events (AEs), and efficacy outcomes. At baseline, and after 16 weeks of treatment, physician-reported severity was measured using the EASI score. Additionally, patient-reported outcome measures (PROMs) were assessed at baseline and at week 16, including a peak score on the Numerical Rating Scale (NRS) for pruritus during the past 7 days, a peak score on the NRS for sleep during the past 7 days, and the Dermatology Life Quality Index (DLQI) score.

Total serum immunoglobulin (Ig) E levels were measured using immunofluorometric assay and expressed in KU/L, according to the manufacturer's instructions. Total IgE normal values were considered to be<100 KU/L. A peripheral blood eosinophil count was also collected. An eosinophil count <500/mm^3 was considered normal.

Study outcomes and statistical analysis

The primary efficacy outcomes included the median percent change in EASI score from baseline to the respective values at week 16, and the proportion of patients achieving a 50%, 75% and 90% improvement in EASI, (EASI-50), (EASI-75), (EASI-90), respectively, from baseline to week 16. The EASI score assesses the severity and extent of erythema; induration, papulation, and oedema; excoriations; and lichenification [12,13]. EASI scores range from 0 to 72, higher scores indicating a greater severity and extent of AD.

Secondary efficacy outcomes included the mean change (baseline to weeks 16) in peak pruritus NRS score during the past 7 days (scores range from 0 to 10, no itch to the worst itch imaginable), mean change in the peak score on NRS for sleep during the past 7 days (scores range from 0 to 10, higher scores indicating a greater effect on sleep disturbances), mean change in scores for DLQI (scores range from 0 to 30, higher scores indicating a greater effect on QoL); a 4-point or higher improvement (reduction) from baseline in peak pruritus NRS during the past 7 days, 4-point

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or higher improvement (reduction) from baseline in DLQI (minimal clinically important difference, MCID).

Characteristics of patients with and without an assessment of outcomes were compared using Student's t-test, Wilcoxon's matched pairs test (in cases of non-normal distribution) for quantitative variables, and Fisher's exact test for qualitative variables. The threshold for statistical significance was set at $p<0.05$. Crude comparisons of the frequencies of the relevant clinical variables associated to treatment response were made with $\chi 2$ test. Variables identified at univariate analysis as potentially relevant predictors ($p<0.1$) were considered in multivariate analyses. A complete case multiple logistic regression model was also considered to estimate adjusted ORs. The procedure started from a full model, including all the variables, except for those predictors having one unique value (zero-variance predictors). A stepwise procedure was carried out to explore the subset of statistically significant predictors. After excluding a number of variables from the analysis, the final stepwise multiple logistic regression model was estimated over n = 468 complete cases. The results were expressed as odds ratio (OR) with 95% confidence interval (CI). All statistical analyses were performed with STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Clinically relevant response

We defined clinically relevant responses based on thresholds of tools commonly used to assess the major AD domains: signs, symptoms, and QoL, as previously reported [14,15]. Patients achieving a clinically relevant improvement in at least one of the three key domains (EASI-75 or NRS pruritus ≥4 point improvement or DLQI ≥4 point improvement) after 16 weeks of dupilumab treatment were considered to show a clinically relevant response. Based on these assessments, those patients who had a complete response to treatment, achieving a clinically relevant improvement in all three key

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domains of clinically relevant responses at week 16, were considered super-responders [14]. Non-responders showed no clinically relevant improvement in the three key domains.

Safety

During treatment, safety was evaluated by recording and monitoring the incidence and severity of AEs and changes in vital signs and clinical laboratory values.

Results

Baseline characteristics

A total of 543 patientswith moderate-to-severe ADrecruited across the 10sitesmet the inclusion criteria, were eligible for the study. The patients were examined by20 different dermatologists in total.

The demographic and clinical characteristics at baseline are presented in Table 1. The median ± interquartile range (IQR) for patient age was 41.0±27.0 years, with females accounting for 43.6% of the cohort. The median±IQR EASI score was 28.0±9.5 points. The median±IQR DLQI score was 17.0±9.0 points.In our cohort, AD had developed before adult age (cut-off value of 18 years) in 366 (67.4%) patients (early-onset AD), whereas in 177 (32.6%), the onset of AD was directly in adulthood (adult-onset AD). The most frequent adult AD phenotype was the classic adult-type with lichenified/exudative flexural dermatitis alone, or associated with head/neck eczema or hand eczema, observed in 301 (55.4%) patients.

Overall, high proportions of 543 patients (345 [63.5%]) had 1 or more allergic comorbidities. The most frequent reported allergic diseases were allergic rhinoconjunctivitis (46.8%), allergic asthma (33.5%), and food allergy (15.5%). Before enrollment, 74.4% of the patients had received CsA, and 89.5% had received systemic glucocorticoids. Before starting the dupilumab treatment, 149 patients (27.4%) had a history of ≥3 immunosuppressive treatments.

Discontinuation of dupilumab

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In our cohort of 543 patients, only 2 patients (0.4%) discontinued treatment before the end of the study period (week 16). One patient discontinued treatment because of bilateral conjunctivitis and cicatricialectropion, which developed halfway through the second month of dupilumab treatment [16].Another patient discontinued because of fever and arthralgia, which started fifteen days after the first dupilumab administration.

Effectiveness of dupilumab treatment

A total of 541/543 (99.6%) patients completed the 16-week treatment period.

EASI-50, EASI-75 and EASI-90 response rates were 98.1%, 81.5%, and 50.8% after 16 weeks ($p<0.001$). The EASI ≤7 (clear-mild AD) response rate was 73.7% after 16 weeks (Table 2).

In our cohort, dupilumab significantly improved themeasures of clinical efficacy and QoL at week 16 (Table 2), including a median ± IQR percentage change from baseline in the EASI score (-87.5±22.0; $p<0.001$), a mean change ± standard error (SE) from baseline in peak score on NRS for pruritus (-5.8±2.6; $p<0.001$), a mean change ± SE from baseline in the peak score on NRS for sleep (-5.9±3.1; $p<0.001$), and a mean change ± SE from baseline in the DLQI score (-13.5±7.2; $p<0.001$).

At 16 weeks, 433 of 543 (80%) patients had achieved a peak pruritus NRS score improvement ≥4 points from baseline; 502 of 541 (92.8%) patients had achieved a 4-point or higher improvement in DLQI from baseline (Table 2).

In 534 of 541 patients (98.7%), a clinically relevant improvement was achieved after 16 weeks of dupilumab treatment.

At the end of the 16-week study, 342 of 541 patients (63.2%) treated with dupilumab showed a clinically meaningful response for all of the major outcome responses and were considered super-responders. Interestingly, no significant differences were found between the proportion of AD patients with the classic adult-type form considered as super-responders (59.2%)

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versus AD patients with the non-classic adult-type form considered super-responders (68.1%) (p>0.01).

Topical corticosteroids and/or topical immunomodulators (tacrolimus and pimecrolimus) were used in 312 patients (96.0%) before starting dupilumab treatment maintaining their use as needed to week 16 in 227 of 541 cases (42%).

The median± IQR serum total IgE, measured in 485 patients, significantly decreased from 753.5±2,855.7 KU/L at baseline to 570±1,510.0KU/L at 16 weeks (p<0.001) (Table 2).

For the median ± IQR total blood eosinophil count, measured in 458 patients, no significant differences from baseline were found by week 16 (340 cell/mm^3±370.3 *vs* 358 cell/mm^3±432; p>0.05) (Table 2). In our cohort, 141 patients (30.8%) were classified as having blood eosinophilia (>500 cell/mm^3) at baseline and 152 (33.2%) at week 16 (p>0.05).

Safety

The overall incidence of adverse events (AEs) during the 16-week treatment phase was 16.4%, the most common AEs being conjunctivitis, headache and arthralgia (Table 3).

Among the 543 patients considered for the treatment, in total 66 (12.2%) subjects were diagnosed with dupilumab-associated conjunctivitis during follow-up after dupilumab administration. Most conjunctivitis cases were considered as mild to moderate and resolved or resolving by the end of week 16. Factors significantly associated with dupilumab-associated conjunctivitis at univariable analysis (Table 4) included a history of conjunctivitis, history of allergic asthma, early AD onset, early dupilumab initiation, high baseline total serum IgE and presence of eosinophilia(>500 eosinophils/mm^3). Interestingly, in the multivariate logistic regression model, the risk of developing dupilumab-related conjunctivitis was associated with early AD onset [OR, 2.25; 95% CI, 1.07–4.70; p = 0.03] and presence of eosinophilia (>500 eosinophils/mm^3) [OR, 1.91; 95% CI, 1.05–3.39; p = 0.03]. Clinical signs and symptoms of conjunctivitis mostly included bulbar and palpebral hyperemia, itching, burning sensation, tearing, foreign body sensation and photophobia. All patients

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with moderate or severe conjunctivitis were referred to an ophthalmologist. Patients with mild conjunctivitis were managed with artificial tears, eye drops/ointment, or oral antihistamines. Topical corticosteroid (TCS) preparations, antibiotic plus TCS combination therapies, topical tacrolimus, and cyclosporin eye drops, were the most frequent therapies recommended by the ophthalmologist.

No treatment-emerging AEs were reported during the study.

Discussion

In adults with moderate-to-severe, difficult-to-treat AD, 16-week dupilumab therapy resulted in statistically significant and clinically meaningful improvements in signs and symptoms of AD.

In our multicenter retrospective study including 543 patients, after 16 weeks of dupilumab treatment, AD lesions, as measured by the EASI score, had significantly improved. The disease-subjective scores (peak pruritus NRS, peak sleep NRS) also showed significant reductions at the end of the 16-week treatment period. For patients with AD, pruritus and sleep loss are among the most important symptoms to be included when addressing treatment response [17]. Improvements in pruritus and sleep are also associated with improvements in QoL [18]; in fact, dupilumab significantly improved QoL in our patients, as assessed by the DLQI.

Dupilumab has been demonstrated to be an effective treatment for patients with moderate-to-severe AD in clinical trials [9-11] and in real-life studies [2,19-33]. To date, there have been some reports on real-world experience with dupilumab, including six multicenter studies [14,19,22-24,26].

In the present study, the effectiveness of dupilumab evaluated by EASI-50 (98%), EASI-75 (81%) and EASI-90 (50%) was higher than the efficacy reported in clinical trials (EASI-50: 65%-85%, EASI-75: 44%-69%, EASI-90: 30-45%) [9-11]. The broadest multicenter study in 241 adult AD patients treated with dupilumab in a real-life setting reported EASI-50 and EASI-75 in 72% and

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48% of the patients, respectively, after three months of treatment [19], which is lower compared to the patients included in our cohort, probably due to the main outcome being assessed at 4 months versus 3 months in our study. Among our cohort, the median percent change in EASI after 16 weeks was -87%, while the least-squares mean percentage change in EASI at week 16 was between -67% and -79% in clinical trials [9-11]. These differences might be due to a population with more severe disease and a higher median score at baseline for EASI in clinical trials. In Faiz's study, the median percent change in EASI after 3 months was -71% [19].

At the 16-week follow-up point of the study, the mean change from baseline in peak score on NRS for pruritus and DLQI was -5.8 and -13.5 points, respectively, while the least-squares mean change from baseline was -3.7 and -9.3 in the SOLO1 trial, -3.3 and -9.3 in the SOLO2 trial, -3.5 and -9.5 points in the CAFE trial, -4.1 and -9.7 in the CHRONOS trial [9-11].

In the cohort described by Faiz et al, the mean change in DLQI after 3 months was -7.3 points [19].

Our real-life study thus elicited higher levels of effectiveness for dupilumab after 16-week treatment than any clinical trial to date. Inevitably, there may be considerable differences in patient characteristics between clinical trials and daily practice and, therefore, results of clinical trials are not always generalizable to daily practice.

In our study, a clinically relevant improvement in at least one of the key domains (EASI-75 or NRS pruritus ≥4 point improvement or DLQI ≥4 point improvement) after 16 weeks of treatment was achieved by 98% of patients, in line with two previous studies that reported a large majority of dupilumab-treated patients (89% and 88%) showing a clinically relevant improvement at week 16 [14, 26].Among our cohort, at week 16, 63% of the patients were classified as super-responders. The definition of complete response/super-responders to dupilumab was suggested by Ariens et al [14]. Although this definition is not the product of a consensus among the community, the clinically relevant response might become a disease measurement tool that can be used to define response to

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dupilumab treatment in patients with AD [14], distinguishing super-responders (patients with an improvement in all the domains) from non-responders (patients with no improvement in any of the domains). In adult AD patients, we can distinguish various clinical forms, although these forms commonly appear together [34]. A remarkable finding in our study is that adult patients with the non-classic adult-type form seem to respond slightly better to dupilumab than patients with classic adult-type form at week 16.

Most of non-classic forms (58%) were seen in more recent, adult-onset cases of AD. Therefore, we can speculate that in these patients there could be a predominantly Th2 activation and an higher IL4/13 activity than in classic, persistent cases [35]. Furthermore, some atypical patterns AD, namely prurigonodularis and nummular eczema, are more frequently diagnosed in elderly patient [36,37], in whom the decline in skin barrier function, dysregulation of innate immune cells, and shift to Th2 profile are reported [38]. These changes have some overlap with recent AD hallmarks and high IL4/13 function. These, hypotheses could explain the slight better, although not significant, efficacy of dupilumab in these patients.

Our patients also experienced a significant decrease in serum IgE at follow-up, in accordance with previous studies [19,20,24,25,28-30,32], since Dupilumab blocks IL-4 and IL-13 which normally cause an increased IgE production [8]. For our cohort of patients, the eosinophil count did not change significantly between baseline and week 16 of follow-up, in line with previously reported data from clinical trials [9-11]. Nevertheless, in the SOLO1 and SOLO2 trials and in the CAFE trial, dupilumab-treated patients had a greater mean initial increase from baseline in the eosinophil count compared to subjects treated with a placebo, then showing subsequent decreases toward or below baseline levels by week 16 [9,10].The findings of these studies differed from those in two other real-life studies, in which the proportions of dupilumab-treated patients who had eosinophilia within six months of follow-up (57%) or within 16 weeks of follow-up (43%) were significantly higher than the proportions at baseline (33%) and (31%), respectively [19-29].The

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increase in blood eosinophil counts is consistent with the hypothesis that dupilumab blocks the migration of eosinophils into tissue by inhibiting IL-4- and IL-13–mediated production of eotaxins (as suggested by a reduction in the serum eotaxin-3 level) and vascular-cell adhesion molecule-1 but not eosinophil production or egress from bone marrow [14]. This action results in a transient increase in circulating eosinophil counts. However, further experimental and clinical studies are needed to confirm this hypothesis.

As regards the safety of dupilumab, new onset conjunctivitis was observed in 66 patients (12.2%). The reported incidence in clinical trials [9-11]and in real-life studies [2,19-33, 39]ranges from 5% to 28%, and from 6% to 62% of dupilumab-treated patients, respectively. During the clinical development of dupilumab in AD [40], the incidence of conjunctivitis was around 10% and infrequent in patients with asthma or nasal polyposis, suggesting that some characteristics of patients with AD may contribute to cause this, as eye involvement can be a comorbidity in AD [41]. Several hypotheses have been proposed for mechanisms driving conjunctivitis in dupilumab-treated patients with AD, including increased OX40 lig and activity involved in atopic keratoconjunctivitis, eosinophilia, decreased IL-13 related mucus production, and increased *Demodex* mites [42]. Predictors of the incidence of dupilumab-associated conjunctivitis are not well known. Increased rates of conjunctivitis have previously been associated with AD severity [9,41,42], a prior history of conjunctivitis [9,41,43], atopic AD phenotype [9,42], and high baseline IgE levels and eosinophil counts [41]. The most remarkable finding in our study is that patients with an early AD onset and presence of eosinophilia (>500 eosinophils/mm^3) seem to be significantly more likely to develop conjunctivitis during dupilumab treatment. AD severity is associated with eosinophil levels as well as with incidence of conjunctivitis, suggesting that the association of this biomarker with conjunctivitis may result from its relationship to AD severity [41].There is no significant difference of AD severity between early vs. adult-onset AD [44] so the reason why an early AD onset is associated with the development of conjunctivitis remains unknown.

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The value provided by this study lies in the need for broader real clinical practice data on dupilumab treatment in patients with moderate-to-severe AD. Limitations include the retrospective nature, short follow-up and lack of control patients.

In conclusion, to date, this is the broadest real-life study in AD patients treated with dupilumab. We observed significant improvements induced by dupilumab in patients with moderate-to-severe, difficult-to-treat AD in a real-world setting, to a greater extent than those reported in clinical trials. Moreover, dupilumab demonstrated a favorable safety profile in our series of adult patients, confirming data obtained in the clinical trials. Further studies are needed to assess the long-term effectiveness and safety of the drug.

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Conflicts of interest

All authors declare that they have no conflicts of interest except for:

- Silvia Mariel Ferrucci is speaker of Novartis and Sanofi Genzyme; she is Principal Investigator for Eli Lilly, Abbvie, Sanofi Genzyme; she is an advisory board member of Sanofi Genzyme
- Luigi Macchia: in the past five years accepted a fee for organizing education
- Caterina Foti: speaker for Sanofi, Abbvie
- Cataldo Patruno: speaker and consultant for AbbVie, Novartis, Pfizer, Sanofi Genzyme
- Franco Rongioletti consultant and Speaker for Abbvie, Sanofi, Janssen, Novartis, Almirall, Lilly
- Eustachio Nettis: in the past five years accepted a fee for organizing education

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Previous presentation

The manuscript has not been published elsewhere and is not under consideration for publication elsewhere.

IRB approval status

Reviewed and approved by the Ethics Committee of Naples Federico II University Hospital, Italy.

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Table 1. Baseline characteristics of patients included in the study (N=543)

Variable	Value*
Age (y)	41.0±27.0
Sex, female	237 (43.6)
Duration of AD (y)	20.0±22.3
EASI score	28.0±9.5
Peak score on NRS for pruritus	9.0±2.0
Peak score on NRS for sleep	8.0±3.0
DLQI score	17.0±9.0
AD pattern	
Early-onset (<18y)	366 (67.4)
Adult-onset (≥18y)	177 (32.6)
AD phenotype	
Classic adult-type‡	301 (55.4)
Non-Classic adult-type§	235 (43.3)
Missing	7 (1.3)
Allergic comorbidities (≥1)	345 (63.5)
Allergic rhinoconjunctivitis	254 (46.8)
Allergic Asthma	182 (33.5)
Food Allergy	84 (15.5)
Previous topical treatments for AD	
Emollients	543 (100.0)
Topical corticosteroids	538 (99.1)
Topical immunomodulators	288 (53.0)
Previous systemic treatments for AD	
Glucocorticoids	486 (89.5)
Cyclosporin A	404 (74.4)
Phototherapy	165 (30.4)

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Methotrexate	33 (6.1)
Omalizumab	11 (2.0)
Alitretinoin	11 (2.0)
Other systemic treatments[†]	17 (3.1)
IgE (KU/L)	753.5±2,855.7
Missing, n (%)	36 (6.6)
Eosinophils (cells/mm^3)	340±370.3
Missing, n (%)	76 (14.0)

Abbreviations: AD, Atopic Dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IQR, Interquartile Range; NRS, Numerical Rating Scale.
*Data are median ±IQR or n (%).
[‡]Classic adult-type: Lichenified/exudative flexural dermatitis alone or associated with head-and-neck eczema and/or hand eczema.
[§]Non-Classic adult-type: generalized eczema (n=106), generalized prurigonodularis (n=52), nummular eczema (n=24), erythroderma (n=16), lichenified/exudative flexural dermatitis associated with portrait dermatitis (n=14), psoriasiform dermatitis (n=10), generalized eczema associated with head-and-neck eczema (n=5), generalized eczema associated with seborrheic dermatitis-like dermatitis (n=2), head-and-neck eczema associated with multiple lesions of chronic lichen simplex (n=2), multiple lesions of chronic lichen simplex (n=1), generalized eczema associated with hand eczema (n=1), generalized eczema associated with psoriasiform dermatitis (n=1), lichenified/exudative flexural dermatitis associated with hand eczema and portrait dermatitis (n=1).
[†]Other systemic treatments: azathioprine (n=7), mofetilmycophenolate (n=7), ustekinumab (n=2), tumor necrosis factor α inhibitors (n=1).
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Table 2. **Patient characteristics at baseline and follow-up after 16 week**

	Baseline (N=543)	Week 16 (N=541)	p-value *
EASI			
Median ±IQR	28±9.5	3.0±6.0	<0.001
Median percent change ±IQR in EASI from baseline		-87.5±22.0	
Mean percent change ±SD in EASI from baseline		-83.8±16.0	
EASI-50, n (%)		531 (98.1)	
EASI-75, n (%)		441 (81.5)	
EASI-90, n (%)		275 (50.8)	
EASI ≤ 7, n (%)		399 (73.7)	
Peak score on NRS for pruritus			
Median ±IQR	9.0±2.0	2.0±4.0	<0.001
Missing, n (%)		1 (0.2)	
Change in peak score on NRS for pruritus from baseline, mean±SD		-5.8±2.6	
Patients who achieved peak pruritus NRS score improvement ≥4 points, n (%)		433 (80)	
Peak score on NRS for sleep			
Median ±IQR	8.0±3.0	0.0±2.0	<0.001
Missing, n (%)		1 (0.2)	
Change in peak score on NRS for sleep from baseline, mean±SD		-5.9±3.1	
DLQI			
Median ±IQR	17.0 ±9.0	2.0±5.0	<0.001
Missing, n (%)		1 (0.2)	
Change in DLQI score from baseline, mean±SD		-13.5±7.2	
Patients with ≥ 4-point improvement in DLQI score, n (%)		502 (92.8)	
Patients with a complete response to treatment (super-responders), n (%)		342 (63.2)	
Total IgE (KU/L)			
Median± IQR	753.5±2,855.7	570±1,510.0	<0.001
Missing, n (%)	36 (6.6)	56 (10.4)	
Eosinophils (cells/mm^3)			
Median ± IQR	340±370.3	358±432.0	>0.05
Missing, n (%)	76 (14.0)	83 (15.3)	

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Abbreviations: AD, Atopic Dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement in EASI score from baseline; EASI-75, ≥75% improvement in EASI score from baseline; EASI-90, ≥90% improvement in EASI score from baseline; IQR, Interquartile Range; NRS, Numerical Rating Scale; SD, Standard Deviation.
Note: Data were compared using Wilcoxon's matched pairs tests and Student t test.
*Comparison between week 16 and baseline.
**Comparison between week 52 and baseline.

Table 3. Adverse events reported by patients receiving dupilumab (N = 543)

Adverse events	**N(%)**
At least 1 adverse event	82 (15.1)
Conjunctivitis	66 (12.2)
Headache	5 (0.9)
Arthralgia	4 (0.7)
Injection-site reaction	1 (0.2)
Asthenia	1 (0.2)
Weight gain	1 (0.2)
Diarrhea	1 (0.2)
Exacerbations of asthma	1 (0.2)
Fever	1 (0.2)
Nausea	1 (0.2)
Orofacial HSV reactivation	1 (0.2)
Any AE leading to discontinuation of study	3 (0.5)

Abbreviations: HSV, *Herpes simplex* virus.

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Table 4. Odds ratio (OR) and 95% confidence interval (CI) fordevelopment of dupilumab-associated conjunctivitis according to baseline characteristics in patients with severe atopic dermatitis

		OR	95%CI	*p* Value[a]
Sex	Females			
	Males	1.0	0.6-1.7	0.9592
Age at dupilumab initiation	≤42 years			
	>42 years	0.5	0.3-0.9	**0.0179**
Duration of AD	≤22 years			
	>22 years	1.4	0.8-2.5	0.2411
Baseline EASI score	≤37.7			
	>37.7	1.3	0.6-2.5	0.5156
Baseline DLQI score	0-20			
	>20	1.4	0.8-2.5	0.2161
Baseline NRS-itch score	≤8			
	>8	1.5	0.8-2.6	0.1558
Baseline NRS-sleep score	≤8			
	>8	1.1	0.6-1.9	0.7189
Early/adult-onset (<18 years)	Adult-onset			
	Early-onset	2.1	1.1-4.4	**0.0171**
Classic adult-type form[b]	No			
	Yes	1.1	0.6-1.9	0.8040
History of allergic	No			
rhinoconjunctivitis	Yes	1.1	0.6-1.9	0.7667
History of allergic asthma	No			
	Yes	1.9	1.1-3.3	**0.0140**
History of conjunctivitis	No			
	Yes	1.9	1.1-3.4	**0.0123**
Number of previous systemic	<3			
immunosuppressive treatments	≥3	1.5	0.8-2.6	0.1501
Baseline total IgE levels	No			
>872 KU/L	Yes	1.9	1.1-3.4	**0.0157**
Eosinophilia	No			
(>500 eosinophils/mm^3)	Yes	1.8	1.0-3.3	**0.0355**

AD, Atopic Dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS-itch, peak pruritus Numerical Rating Scale; NRS-sleep, peak sleep Numerical Rating Scale.

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[a]Significant*p* Values are shown in bold (*P*-values are statistically significant at a threshold of 5%).

[b]Lichenified/exudative flexural dermatitis alone or associated with head-and-neck eczema and/or hand eczema.

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