ORIGINAL ARTICLE

Use of Dupilumab in 543 Adult Patients With Moderate-to-Severe Atopic Dermatitis: A Multicenter, Retrospective Study

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Abstract

Background: Dupilumab has proven to be an effective treatment for patients with moderate-to-severe atopic dermatitis (AD) in clinical trials. However, real-world experience with dupilumab in a broader population is limited.
Methods: The study population comprised adult patients with moderate-to-severe AD, defined as an Eczema Area Severity Index (EASI) score of 24 or higher, treated with dupilumab at 10 Italian teaching hospitals. We analyzed physician-reported outcome measures (EASI), patient-reported outcome measures (pruritus and sleep score, Dermatology Life Quality Index [DLQI]), and serological markers (IgE and eosinophil count) after 16 weeks.
Results: We enrolled 543 patients with moderate-to-severe AD. Two patients (0.4%) discontinued treatment. The median (IQR) change from baseline to 16 weeks of treatment in the EASI score was –87.5 (22.0) (P<.001). The 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 treatment with dupilumab, 12.2% of the patients developed conjunctivitis, and total IgE decreased significantly (P<.001). Interestingly, in the multivariate logistic regression model, the risk of developing dupilumab-related conjunctivitis was associated with early onset of AD (OR, 2.25; 95%CI, 1.07-4.70; P=.03) and presence of eosinophilia (OR, 1.91; 95%CI, 1.05-3.39; P=.03).
Conclusion: This is the broadest real-life study in AD patients treated with dupilumab to date. We observed more significant improvements induced by dupilumab in adult patients with moderate-to-severe AD than those reported in clinical trials.

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

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 de -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.

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 children in most countries around the world [1]. Affected patients experience persistent or relapsing skin lesions associated with a spectrum of atopic comorbidities [2]. AD negatively impacts patients' quality of life (QOL) in health-related aspects such as physical, psychosocial, and mental functioning [3]. Key features of affected skin in AD patients include skin barrier defects, impaired cornified envelope formation, and aberrant keratinocyte differentiation [4]. AD is also characterized by increased expression of the T2 cytokine axis, in which 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 is often difficult to control 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 competitive binding to the shared α subunit of the IL-4 receptor [8]. Blockade of IL-4/13 is effective in reducing the T helper (T_H) 2 response.

Dupilumab is the first biologic agent to have been approved for the treatment of patients with inadequately controlled moderate-to-severe AD. The efficacy and safety of dupilumab have been investigated in 3 main placebo-controlled phase 3 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 2 trials [9,10] found a significant improvement in measures of skin clearing and overall disease severity at 16 weeks of treatment, and the third [11] found a significant improvement in overall disease severity at 16 and 52 weeks.

As data on dupilumab in a real-world setting are limited, it is important to assess the administration of this treatment in daily clinical practice and in a broader population. We studied 543 Italian adult patients with moderate-to-severe, difficult-to-treat AD treated with dupilumab. Herein, we report our real-world data on treatment with dupilumab.

Methods

Study Design and Participants

We performed a multicenter retrospective chart review including adult patients with moderate-to-severe AD who had started dupilumab as standard care from September 2018 to April 2020 at 10 Italian university allergology/dermatology centers. Dupilumab was prescribed according to the recommendations of the Italian Drug Agency (AIFA). In order to participate in this study, each center had to provide data on patients aged 18 years and older who had moderate-to-severe AD, defined as an Eczema Area Severity Index (EASI) score of 24 or higher, and an inadequate response to/intolerance of cyclosporine 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 Declaration of Helsinki 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 their written informed 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 every other week.

A washout period was not required. Any approved topical AD treatments were permitted as needed, or 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 pretreatment for the management of atopic comorbidities.

We recorded the clinical history, demographics, allergic comorbidities (ie, allergic rhinoconjunctivitis, allergic asthma, and food allergy), concomitant medications or procedures, adverse events, 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 were assessed at baseline and at week 16, including the peak score on the Numerical Rating Scale (NRS) for pruritus during the previous 7 days, the peak score on the NRS for sleep during the previous 7 days, and the Dermatology Life Quality Index (DLQI) score.

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

Study Outcomes and Statistical Analysis

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

Secondary efficacy outcomes included the mean change (baseline to week 16) in the peak pruritus NRS score during the past 7 days (scores range from 0 to 10, no itch to the worst itch imaginable), the mean change in the peak score on the NRS for sleep during the past 7 days (scores range from 0 to 10, higher scores indicating a greater effect on sleep disturbances), the mean change in scores for DLQI (scores range from 0 to 30, higher scores indicating a greater effect on QOL), a ≥4-point improvement (reduction) from baseline in peak NRS for pruritus during the previous 7 days, and a ≥4-point improvement (reduction) from baseline in DLQI (minimal clinically important difference).

Characteristics of patients with and without an assessment of outcomes were compared using the *t* test, the Wilcoxon matched pairs test (in the case of a nonnormal distribution) for quantitative variables, and the Fisher exact test for qualitative variables. The threshold for statistical significance was set at $P<.05$. Crude comparisons of the frequencies of the relevant clinical variables associated with treatment response were made using the χ^2 test. Variables identified in the univariate analysis as potentially relevant predictors ($P<.1$) were included in the multivariate analyses. A complete-case multiple logistic regression model was also run to estimate adjusted ORs. The procedure started from a full model, including all the variables, except those predictors with 1 unique value (zero-variance predictors). A stepwise procedure was carried out to explore the subset of statistically

Table 1. Baseline Characteristics of Patients Included in the Study (N=543)

Variable	Value[a]
Age, y	41.0 (27.0)
Sex, female	237 (43.6)
Median (IQR) duration of AD, y	20.0 (22.3)
Median (IQR) EASI score	28.0 (9.5)
Median (IQR) peak score on NRS for pruritus	9.0 (2.0)
Median (IQR) peak score on NRS for sleep	8.0 (3.0)
Median (IQR) DLQI score	17.0 (9.0)
AD pattern	
Early-onset (<18 y)	366 (67.4)
Adult-onset (≥18 y)	177 (32.6)
AD phenotype	
Classic adult-type[b]	301 (55.4)
Nonclassic adult-type[c]	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	
Corticosteroids	486 (89.5)
Cyclosporine A	404 (74.4)
Phototherapy	165 (30.4)
Methotrexate	33 (6.1)
Omalizumab	11 (2.0)
Alitretinoin	11 (2.0)
Other systemic treatments[d]	17 (3.1)
Median (IQR) IgE, kU/L	753.5 (2855.7)
Missing, No. (%)	36 (6.6)
Eosinophils, cells/mm^3	340 (370.3)
Missing, No. (%)	76 (14.0)

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale.

[a]Data are shown as median (IQR) or No. (%).

[b]Classic adult-type: lichenified/exudative flexural dermatitis alone or associated with head-and-neck eczema and/or hand eczema.

[c]Nonclassic adult-type: generalized eczema (n=106), generalized prurigo nodularis (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).

[d]Other systemic treatments: azathioprine (n=7), mycophenolate mofetil (n=7), ustekinumab (n=2), tumor necrosis factor α inhibitors (n=1).

significant predictors. After excluding several variables from the analysis, the final stepwise multiple logistic regression model was based on 468 complete cases. The results were expressed as the OR with the 95%CI. All statistical analyses were performed using STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12).

Clinically Relevant Response

We defined clinically relevant responses based on the 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 1 of the 3 key domains (EASI-75 or NRS pruritus ≥4-point improvement or DLQI ≥4-point improvement) after 16 weeks of dupilumab were considered to show a clinically relevant response. Based on these assessments, patients who had a complete response to treatment, achieving a clinically relevant improvement in all 3 key domains of clinically relevant responses at week 16, were considered superresponders [14]. Nonresponders showed no clinically relevant improvement in the 3 key domains.

Safety

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

Table 2. Patient Characteristics at Baseline and at 16 Weeks

	Baseline (N=543)	Week 16 (N=541)	*P* Value[a]
Median (IQR) EASI	28 (9.5)	3.0 (6.0)	<.001
Median (IQR) percent change in EASI from baseline		–87.5 (22.0)	
Mean (SD) percent change in EASI from baseline		–83.8 (16.0)	
EASI-50, No. (%)		531 (98.1)	
EASI-75, No. (%)		441 (81.5)	
EASI-90, No. (%)		275 (50.8)	
EASI ≤7, No. (%)		399 (73.7)	
Peak score on NRS for pruritus Median (IQR) Missing, No. (%)	9.0 (2.0)	2.0 (4.0) 1 (0.2)	<.001
Mean (SD) change in peak score on NRS for pruritus from baseline		–5.8 (2.6)	
Patients with a peak pruritus NRS score improvement ≥4 points, No. (%)		433 (80)	
Peak score on NRS for sleep Median (IQR) Missing, No. (%)	8.0 (3.0)	0.0 (2.0) 1 (0.2)	<.001
Mean (SD) change in peak score on NRS for sleep from baseline		–5.9 (3.1)	
DLQI Median (IQR) Missing, No. (%)	17.0 (9.0)	2.0 (5.0) 1 (0.2)	<.001
Mean (SD) change in DLQI score from baseline		–13.5 (7.2)	
Patients with ≥4-point improvement in DLQI score, No. (%)		502 (92.8)	
Patients with a complete response to treatment (super-responders), No. (%)		342 (63.2)	
Total IgE (kU/L) Median (IQR) Missing, No. (%)	753.5 (2855.7) 36 (6.6)	570 (1510.0) 56 (10.4)	<.001
Eosinophils/mm^3 Median (IQR) Missing, No. (%)	340 (370.3) 76 (14.0)	358 (432.0) 83 (15.3)	>.05

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; NRS, Numerical Rating Scale.
Note: Data were compared using the Wilcoxon matched pair test and the *t* test.
[a]Comparison between week 16 and baseline.

Results

Baseline Characteristics

A total of 543 patients with moderate-to-severe AD recruited across the 10 sites met the inclusion criteria and were eligible for the study. The patients were examined by 20 different dermatologists in total.

The demographic and clinical characteristics at baseline are presented in Table 1. The median (IQR) patient age was 41.0 (27.0) years, with females accounting for 43.6% of the cohort. The median EASI score was 28.0 (9.5) points. The median DLQI score was 17.0 (9.0) points. We found that AD had developed before adulthood (cut-off value of 18 years) in 366 patients (67.4%) (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 (301 patients [55.4%]).

Many of the 543 patients (345 [63.5%]) had ≥1 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 corticosteroids. Before starting dupilumab, 149 patients (27.4%) had received ≥3 immunosuppressive treatments.

Discontinuation of Dupilumab

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 cicatricial ectropion, which developed halfway through the second month [16]. Another patient discontinued because of fever and arthralgia, which started 15 days after the first dose of dupilumab.

Effectiveness of Dupilumab

A total of 541/543 patients (99.6%) 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<.001). The EASI ≤7 (clear-mild AD) response rate was 73.7% after 16 weeks (Table 2).

In our cohort, dupilumab significantly improved the measures of clinical efficacy and QOL at week 16 (Table 2), including a median percentage change from baseline in the EASI score (–87.5 [22.0]; P<.001), a mean (SE) change from baseline in the peak score in the NRS for pruritus (–5.8 [2.6]; P<.001), a mean change from baseline in the peak score in the NRS for sleep (–5.9 [3.1]; P<.001), and a mean change from baseline in the DLQI score (–13.5 [7.2]; P<.001).

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

Table 3. Adverse Events Reported by Patients Receiving Dupilumab (N=543)

Adverse events	No. (%)
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 adverse event leading to discontinuation of study	3 (0.5)

Abbreviations: HSV, *Herpes simplex* virus.

At the end of the 16-week study, 342 of 541 patients (63.2%) treated with dupilumab showed a clinically meaningful response for all the major outcome responses and were considered superresponders. Interestingly, no significant differences were found between the proportion of AD patients with the classic adult type considered as superresponders (59.2%) and AD patients with the nonclassic adult type considered superresponders (68.1%) (P>.01).

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

The median serum total IgE, which was measured in 485 patients, decreased significantly from 753.5 (2855.7) kU/L at baseline to 570 (1510.0) kU/L at 16 weeks (P<.001) (Table 2).

No significant differences from baseline were found by week 16 for the median (IQR) total blood eosinophil count, which was measured in 458 patients (340/mm^3 [370.3] vs 358/m^3 [432]; P>.05) (Table 2). In our cohort, blood eosinophilia (>500/mm^3) was recorded in 141 patients (30.8%) at baseline and in 152 (33.2%) at week 16 (P>.05).

Safety

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

Of the 543 patients considered for the treatment, 66 (12.2%) were diagnosed with dupilumab-associated conjunctivitis during follow-up. Most cases of conjunctivitis were considered mild to moderate and resolved or were resolving by the end of week 16. Factors significantly associated with dupilumab-associated conjunctivitis in the univariate analysis (Table 4) included a history of conjunctivitis, history of allergic asthma, early-onset AD, early initiation of dupilumab, high baseline total serum

IgE, and presence of eosinophilia (>500/mm^3). Interestingly, the multivariate logistic regression model showed the risk of developing dupilumab-related conjunctivitis to be associated with early-onset AD (OR, 2.25; 95%CI, 1.07-4.70; *P*=.03) and presence of eosinophilia (>500/mm^3) (OR, 1.91; 95%CI, 1.05-3.39; *P*=.03). Clinical signs and symptoms of conjunctivitis mostly included bulbar and palpebral hyperemia, itching, burning sensation, tearing, foreign body sensation, and photophobia. All patients with moderate-to-severe conjunctivitis were referred to an ophthalmologist. Patients with mild conjunctivitis were managed with artificial tears, eye drops/ointment, and oral antihistamines. The most frequent therapies recommended by the ophthalmologist were topical corticosteroid preparations, antibiotics plus topical corticosteroid combinations, topical tacrolimus, and cyclosporine eye drops.

No treatment-emergent adverse events were reported during the study.

Discussion

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

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

Table 4. OR and 95%CI for Development 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	.9592
Age at initiation of dupilumab	≤42 y			
	>42 y	0.5	0.3-0.9	.0179
Duration of AD	≤22 y			
	>22 y	1.4	0.8-2.5	.2411
Baseline EASI score	≤37.7			
	>37.7	1.3	0.6-2.5	.5156
Baseline DLQI score	0-20			
	>20	1.4	0.8-2.5	.2161
Baseline NRS for pruritus	≤8			
	>8	1.5	0.8-2.6	.1558
Baseline NRS for sleep	≤8			
	>8	1.1	0.6-1.9	.7189
Early/adult-onset (<18 years)	Adult-onset			
	Early-onset	2.1	1.1-4.4	.0171
Classic adult-type[b]	No			
	Yes	1.1	0.6-1.9	.8040
History of allergic rhinoconjunctivitis	No			
	Yes	1.1	0.6-1.9	.7667
History of allergic asthma	No			
	Yes	1.9	1.1-3.3	.0140
History of conjunctivitis	No			
	Yes	1.9	1.1-3.4	.0123
Number of previous systemic immunosuppressive treatments	<3			
	≥3	1.5	0.8-2.6	.1501
Baseline total IgE levels >872 kU/L	No			
	Yes	1.9	1.1-3.4	.0157
Eosinophilia >500/mm^3	No			
	Yes	1.8	1.0-3.3	.0355

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale.
[a]Significant *p* Values are shown in bold (*P*<.05).
[b]Lichenified/exudative flexural dermatitis alone or associated with head-and-neck eczema and/or hand eczema.

Dupilumab has proven 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 reports of real-world experience with dupilumab, including 6 multicenter studies [14,19,22-24,26].

Based on EASI-50 (98%), EASI-75 (81%), and EASI-90 (50%), dupilumab was more effective in our study than 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 48% of patients, respectively, after 3 months of treatment [19], that is, lower than in the patients included in our cohort, probably owing to the main outcome being assessed at 4 months compared with 3 months in our study. In the present 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 EASI score at baseline in clinical trials. In the study by Faiz et al [19], the median percent change in EASI after 3 months was –71% [19].

At the 16-week follow-up point, 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 [19], the mean change in DLQI after 3 months was –7.3 points.

Our real-life study thus indicated greater effectiveness for dupilumab after a 16-week course of treatment than any clinical trial to date. Inevitably, there may be considerable differences in patient characteristics between clinical trials and daily practice, thus preventing trial results from being generalized to daily practice.

In our study, a clinically relevant improvement in at least 1 of the key domains (≥4-point improvement in EASI-75, NRS pruritus, or DLQI) after 16 weeks of treatment was achieved by 98% of patients, in line with 2 previous studies reporting a clinically relevant improvement at week 16 in a large majority of dupilumab-treated patients (89% and 88%) [14,26]. We classified 63% of patients as superresponders at week 16. The definition of complete response/superresponse to dupilumab was suggested by Ariens et al [14]. While not a consensus-based definition, the clinically relevant response might become a disease measurement tool that can be used to define response to dupilumab in patients with AD [14], distinguishing superresponders (patients with an improvement in all the domains) from nonresponders (patients with no improvement in any of the domains). In adult AD patients, we can distinguish between various clinical forms, although these forms commonly appear together [34]. A remarkable finding in our study is that adult patients with the nonclassic adult-type disease seem to respond slightly better to dupilumab than patients with the classic adult-type disease at week 16.

Most nonclassic forms (58%) were seen in more recent, adult-onset AD. Therefore, we can speculate that in these patients, T_H2 activation is predominant and IL-4 and IL-13 activity higher than in classic, persistent cases [35]. Furthermore, some atypical AD patterns, namely, prurigo nodularis and nummular eczema, are more frequently diagnosed in elderly patients [36,37], who experience a decline in skin barrier function, dysregulation of innate immune cells, and a shift to a T_H2 profile [38]. These changes may overlap with recent AD hallmarks and marked IL-4 and IL-13 function. The hypotheses put forward above could explain the slightly better—albeit not significant—efficacy of dupilumab in affected patients.

Consistent with previous studies [19,20,24,25,28-30,32], patients in the present study also experienced a significant decrease in serum IgE at follow-up, since dupilumab blocks IL-4 and IL-13, which normally lead to increased IgE production [8]. We found that the eosinophil count did not change significantly between baseline and week 16, in line with data from clinical trials [9-11]. Nevertheless, in the SOLO1 and SOLO2 trials and in the CAFE trial, dupilumab-treated patients experienced a greater mean initial increase from baseline in eosinophil count than individuals who received placebo and subsequently experienced decreases toward or below baseline levels by week 16 [9,10]. The findings of these studies differed from those in 2 other real-life studies, in which the proportions of dupilumab-treated patients who had eosinophilia within 6 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 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 for 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, respectively, from 5% to 28% and from 6% to 62% of dupilumab-treated patients. During the clinical development of dupilumab for AD [40], the incidence of conjunctivitis was around 10% and infrequent in patients with asthma or nasal polyposis, possibly because of some characteristics of patients with AD, since 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 the increased OX40 ligand 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 severity of AD [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 was that patients with early-onset AD and eosinophilia (>500 eosinophils/mm^3) seem to be significantly more likely to develop conjunctivitis during treatment with dupilumab. The severity of AD is associated with eosinophil levels and incidence of conjunctivitis, suggesting that the association between eosinophil count and conjunctivitis may result from

their relationship with severity of AD [41]. As there is no significant difference in severity of AD between early- and adult-onset disease [44], the reason why early-onset AD is associated with conjunctivitis remains unknown.

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

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

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Conflicts of Interest

Silvia Mariel Ferrucci has been a speaker for Novartis and Sanofi Genzyme. She has also been a Principal Investigator for Eli Lilly, AbbVie, and Sanofi Genzyme and has served on advisory boards for Sanofi Genzyme.

In the past 5 years, Luigi Macchia has received fees for organizing educational programs.

Caterina Foti has been a speaker for Sanofi and AbbVie.

Cataldo Patruno has been a speaker and consultant for AbbVie, Novartis, Pfizer, and Sanofi Genzyme.

Franco Rongioletti has acted as a consultant and speaker for AbbVie, Sanofi, Janssen, Novartis, Almirall, and Lilly.

During the past 5 years, Eustachio Nettis has received fees for organizing educational programs.

The remaining authors declare that they have no conflicts of interest.

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