Received: 21 January 2020 | Revised: 15 March 2020 | Accepted: 31 March 2020

DOI: 10.1111/all.14338

ORIGINAL ARTICLE

Allergen-Specific Immunotherapy and Biologics

Efficacy of dupilumab in atopic comorbidities associated with moderate-to-severe adult atopic dermatitis

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Abstract

Background: Dupilumab is an anti-IL-4Rα antibody used in the treatment of patients with moderate-to-severe atopic dermatitis (msAD).

This study explored the potential benefit of dupilumab in perennial allergic rhinoconjunctivitis (PAR) and perennial allergic asthma (PAA) caused by indoor allergens in adults with msAD.

Methods: This multicentric, prospective, observational, real-life study included adult patients with msAD who had been treated with dupilumab in 16 Italian care centres. Efficacy outcomes regarding AD, PAR and PAA were collected at baseline and 16 weeks. Safety was also assessed.

Results: We enrolled 123 patients with msAD. Between baseline and 16 weeks of treatment, the following measurements decreased statistically significantly: Eczema Area and Severity Index, SCOring AD, Patient-Oriented Eczema Measure, pruritus score, sleep score, Dermatology Life Quality Index and IgE.

Dupilumab treatment in patients with comorbid PAR (n = 41) was associated with significant improvements in PAR disease control (measured using a Rhinitis Control Scoring System) and in PAR Quality of life (QoL) (measured using the Rhinoconjunctivitis QoL Questionnaire scores).

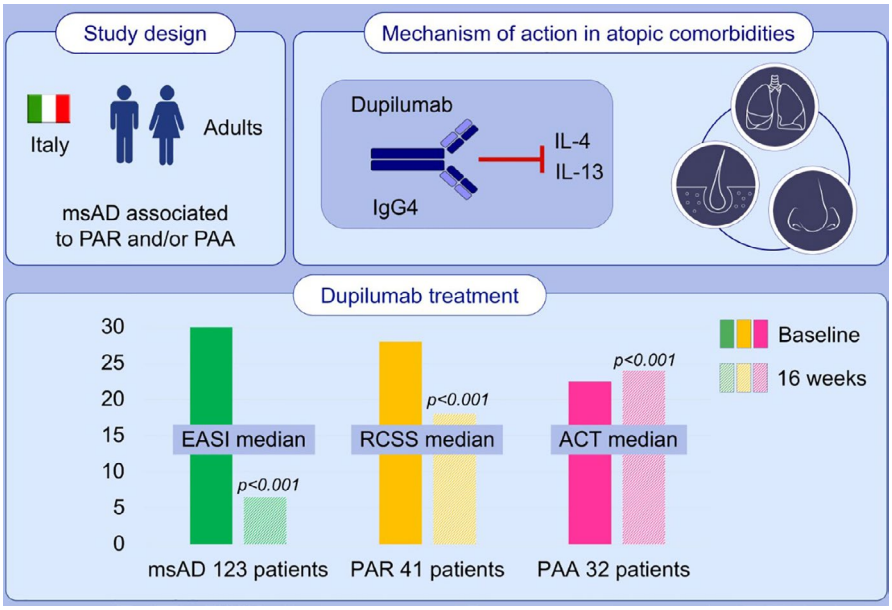
In 32 patients with comorbid PAA, dupilumab significantly improved PAA control (measured using the Asthma Control Test and five-item Asthma Control Questionnaire scores) and disease-related QoL (measured using the Asthma QoL Questionnaire scores). Thirty-five patients (28.5%) developed conjunctivitis during the study period.

Conclusion: These results support the benefits of dupilumab for adult patients with PAR and/or PAA associated with msAD.

KEYWORDS

atopic comorbidities, atopic dermatitis, dupilumab, multicentric real-life study

The members of Italian DADReL study group are listed in Appendix 1.



GRAPHICAL ABSTRACT

This study explores the potential benefit of dupilumab in perennial allergic rhinoconjunctivitis (PAR) and perennial allergic asthma (PAA) caused by indoor allergens in adults with moderate-to-severe atopic dermatitis (msAD). These results support the benefits of dupilumab for adult patients with PAR and/or PAA associated with msAD. In addition, dupilumab treatment significantly improves disease severity and quality of life in patients with msAD.

Abbreviations: ACT, asthma control test; EASI, eczema area severity index; msAD, moderate-to-severe atopic dermatitis; PAA, perennial allergic asthma; PAR, perennial allergic rhinoconjunctivitis; QoL, quality of life; RCSS, rhinitis control scoring system.

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic skin disorder that usually begins in childhood.[1] Although the majority of childhood AD spontaneously resolves by adulthood, the disease persists in 10%-30% of cases.[2] More rarely, the first symptoms develop in adulthood, and the prevalence of AD in adults is approximately 1%-3%.[3-5] AD is associated with a substantial patient burden and a spectrum of atopic comorbidities, including asthma, allergic rhinitis, allergic conjunctivitis, atopic keratoconjunctivitis, chronic rhinosinusitis, food allergies and oeosinophilic esophagitis, as well as nonatopic comorbidities, including several primarily neuropsychiatric disorders.[6] Several US population-based studies have examined the prevalence of atopic comorbidities in AD. In adults, lifetime and one-year prevalence of self-reported asthma was 25.5% and 18.7%, respectively; the one-year prevalence of allergic rhinitis was 28.45%.[7] Lifetime prevalence of asthma and allergic rhinitis increases in adults with more severe AD.[8] While these associations are widely recognized, the mechanisms behind them are still a topic of debate. To date, the majority of research into the links between AD and respiratory allergies has focused on using the existence of a supposed "atopic march" of allergic symptoms in order to establish causal mechanisms. "Atopic march" refers to the childhood progression of symptoms from AD to asthma to allergic rhinitis.[9] The predominant hypothesis for this progression is that, in susceptible individuals, a defect in skin barrier function creates type 2 inflammatory responses to respiratory environmental, food and bacterial allergens. This results in multiple IgE sensitization and high IgE that predispose to subsequent development of allergic diseases.[10] Patient burden and comorbidities should be taken into account when evaluating and managing AD patients' treatment, and this might improve therapeutic decision-making and patient outcomes.

Dupilumab is a fully human monoclonal IgG4 antibody that binds to the shared alpha subunit of the IL-4 receptor and thereby inhibits IL-4 and IL-13 signal transduction.[11] These cytokines are primarily produced by Th2 cells and are central to the pathogenesis of AD and other atopic diseases.[12]

Because patients with AD have high rates of comorbid type 2 diseases, in this multicentric, prospective, observational, real-life study we explored the potential benefit of dupilumab in perennial allergic rhinoconjunctivitis (PAR) and perennial allergic asthma (PAA) due to indoor allergens (eg dust mites, mould and animal dander)[13] in adults with moderate-to-severe atopic dermatitis (msAD).

2 | METHODS

2.1 | Patient population and study design

Sixteen Italian secondary care centres for allergy and clinical immunology, all of which were part of Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC) taskforce, were involved in this observational, prospective study between September 2018 and October 2019.

In order to participate in this study, each centre had to provide data on patients aged 18 years and older with msAD, defined as

having a score of 3 (moderate) or 4 (severe) on the Investigator's Global Assessment (IGA) and an Eczema Area Severity Index (EASI) score of 24 or greater, 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 Italian Drug Agency (AIFA) for patient enrolment. Patients included in the study had also not responded adequately to topical treatments.

All procedures complied with the Helsinki Declaration of 1964, revised in 2013. The study protocol (number 161/19) was approved by the ethical committee of Naples University Hospital, Italy. Informed consent was obtained from all patients who agreed to participate in this study.

All patients were treated with a 600 mg loading dose and subsequent biweekly 300 mg injections of dupilumab for 16 weeks.

A wash-out period was not required. Patients were asked to discontinue systemic immunosuppressants before the start of dupilumab treatment, and rescue treatment for AD could be provided to patients at the investigators' discretion. Throughout the study period, patients were required to maintain their pretreatment therapy for the management of atopic comorbidities.

Patients were assessed for medical history, demographics, comorbid type 2 immune diseases (ie allergic rhinoconjunctivitis, asthma, chronic rhinosinusitis with and without polyposis, food allergies and oeosinophilic esophagitis), concomitant medications or procedures, adverse events and efficacy outcomes at baseline. Safety and efficacy were assessed every four weeks starting at week four.

2.2 | Study endpoints and statistical analysis

AD and atopic comorbidities were evaluated using EASI score (range: 0-72), SCOring AD (SCORAD) (range: 0-103), IGA (range: 0-4), Patient-Oriented Eczema Measure (POEM) (range: 0-30), peak score on the Numerical Rating Scale (NRS) for pruritus (range: 0-10), peak score on the Numerical Rating Scale (NRS) for sleep (range: 0-10), Dermatology Life Quality Index (DLQI) (range: 0-28), Rhinitis Control Scoring System (RCSS) (range: 10-50), Rhinitis Control Scoring System (RCSS) (range: 0-6), Spirometry, Asthma Control Test (ACT) (range: 0-25), five-item Asthma Control Questionnaire (ACQ-5) (range: 0-6), Asthma Quality of Life Questionnaire (standardized version) (AQLQ[S]) (range: 0-7) and complete ear, nose and throat (ENT) examinations. Within-patient improvement in RQLQ, ACT, ACQ-5 and AQLQ(S) scores of at least 0.5, 3, 0.5 or 0.5, respectively, was considered clinically meaningful, as defined by the questionnaire developers.[14-18] Controlled asthma was defined as asthma with a composite of ACT score of more than 19, and the absence of exacerbations during the 16-week treatment period.[15]

Skin prick tests using commonly available foods and inhalants were performed on all patients. Total serum IgE levels were measured using immunofluorometric assay and expressed in KUA/L, according to the manufacturer's instructions. A peripheral blood oeosinophil count was also collected.

Characteristics of patients with and without an assessment of outcomes were compared using Student's *t* tests, Wilcoxon tests (in cases of non-normality) for quantitative variables and Fisher's exact tests for qualitative variables. All statistical analyses were performed with SPSS version 20. The threshold for statistical significance was set at $P < .05$.

3 | RESULTS

A total of 123 patients with msAD who received at least one dose of dupilumab at the study centres between September 2018 and October 2019 were included in the study. The patients were examined by 46 different physicians in total.

In brief, 51 patients (41.5%) were female and the median ± interquartile range (IQR) for patient age was 34.0 ± 21.0 years. The median ± IQR score was 30.0 ± 11.9 for EASI. A total of 95 (77.2%) had severe AD (IGA score 4), while 28 (22.8%) had moderate AD (IGA score 3). Before enrolment, 24 patients (19.5%) had received systemic glucocorticoids. Ninety-three patients (75.6%) had positive prick test results. Comorbid type 2/Th2 immune diseases were common. The demographic and clinical characteristics at baseline are presented in Table 1.

In our cohort of 123 patients, one discontinued treatment because of bilateral conjunctivitis and cicatricial ectropion.

3.1 | Atopic dermatitis

In the remaining 122 patients with msAD, dupilumab significantly improved measures of clinical efficacy and quality of life (QoL) at week 16 (Table 2), including a median ± IQR percentage change from baseline in the EASI score (−81.6 ± 23.0; $P < .001$), median ± IQR percentage change from baseline in the SCORAD score (−73.1 ± 23.6; $P < .001$), a mean change ± SE from baseline in the POEM score (−11.5 ± 8.0; $P < .001$), mean change ± SE from baseline in peak score on NRS for pruritus (−5.9 ± 2.0; $P < .001$), a mean change ± SE from baseline in the peak score on NRS for sleep (−5.6 ± 2.8; $P < .001$) and a mean change ± SE from baseline in the DLQI score (−12.8 ± 6.2; $P < .001$).

At 16 weeks, 60 of 122 (49.2%) patients had achieved an IGA score of 0/1 and a reduction of ≥2 points from baseline ($P < .001$); 80 of 122 (65.6%) patients had achieved ≥75% improvement from baseline as measured by EASI score (EASI-75) ($P < .001$). The percentage of patients who were receiving daily oral corticosteroids (OCS) significantly decreased from 19.7% to 2.4% ($P < .001$). The mean ± SD prednisone equivalent dose was 8.0 ± 5.2 mg at baseline (in 24 patients) and 8.3 ± 4.7 mg at week 16 (in three patients).

The median ± IQR serum total IgE, measured in 112 patients, significantly decreased from 947 ± 3778.3 KUA/L at baseline to 765 ± 2613.5 KUA/L at 16 weeks ($P < .001$) (Table 2).

TABLE 1 Characteristics of patients included in the study (N = 123)

Variable	Value*
Age (y)	34.0 ± 21.0
Sex, female	51 (41.5%)
Duration of AD (y)	18.0 ± 19.0
EASI score	30.0 ± 11.9
SCORAD-total score	69.9 ± 18.7
IGA score of 4	95 (77.2%)
IGA score of 3	28 (22.8%)
POEM score	19.0 ± 9.0
Peak score on NRS for pruritus	9.0 ± 3.0
Peak score on NRS for sleep	8.0 ± 3.5
DLQI score	16.0 ± 9.0
Positive skin prick test results	93 (75.6%)
Allergic rhinitis	74 (60.2%)
RCSS score	28.0 ± 12.3
RQLQ score	2.3 ± 1.5
Allergic conjunctivitis	29 (23.6%)
Atopic keratoconjunctivitis	6 (4.9%)
Chronic rhinosinusitis	12 (9.8%)
Polyposis	6 (4.9%)
Allergic Asthma	58 (47.2%)
FEV1 (L)	3.44 ± 0.90
FEV1 (% predicted)	92.8 ± 16.5
ACT score	24.0 ± 6.2
ACQ-5 score	0.9 ± 1.7
AQLQ (S) score	5.9 ± 2.3
Controlled asthma[a]	41 (70.4%)
Food Allergy	31 (25.2%)
Oral allergy syndrome	9 (7.3%)
Urticaria	20 (16.3%)
Anaphylactic shock	2 (1.6%)
Oeosinophilic esophagitis	0 (0%)
Use of systemic Immunosuppressants for AD	9 (7.3%)
Use of oral glucocorticoids for AD	
Maintenance use	24 (19.5%)
Median daily dose mg[b]	5.0 ± 5.0
IgE (KUA/L)[c]	959 ± 3701
Oeosinophils (cells/mm^3)[d]	377 ± 355.5

Abbreviations: ACQ-5, Asthma Control Questionnaire (5 items); ACT, Asthma Control Test; AD, Atopic Dermatitis; AQLQ (S), Asthma Quality of Life Questionnaire (standardized version); DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; FEV1, Forced Expiratory Volume in 1 second;IGA, Investigator's Global Assessment; IQR, Interquartile Range; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; RCSS, Rhinitis Control Scoring System; RQLQ, Rhinitis Quality of Life Questionnaire; SCORAD, SCORing Atopic Dermatitis.

* Data are median ± IQR or n (%).

[a]The percentage was calculated among the 58 patients who had allergic asthma.

[b]The list value is prednisone equivalent.

[c]Performed in 113 patients.

[d]Performed in 115 patients.

TABLE 2 Change in outcome measures between baseline and 16 weeks for AD patients treated with dupilumab (n = 122)

Outcome	Baseline	Week 16	*P*-value[a]
EASI			
Median ± IQR	30 ± 11.9	6.5 ± 6.5	<.001
SCORAD			
Median ± IQR	69.9 ± 18.8	19.8 ± 15.0	<.001
IGA			
Median ± IQR	4.0 ± 0.0	2.0 ± 1.0	<.001
POEM			
Median ± IQR	19.0 ± 9.0	5.0 ± 5.0	<.001
Peak pruritus NRS			
Median ± IQR	9.0 ± 3.0	2.0 ± 2.0	<.001
Peak sleep NRS			
Median ± IQR	8.0 ± 3.0	1.0 ± 3.0	<.001
DLQI			
Median ± IQR	16.0 ± 9.0	3.5 ± 4.0	<.001
IGA score of 0/1 and reduction ≥2 points, n (%)		60 (49.2)	<.001
EASI75, n (%)		80 (65.6)	<.001
Total IgE (KUA/L)[b]			
Median ± IQR	947 ± 3778.3	765 ± 2613.5	<.001
Oeosinophils (cells/mm^3)[c]			
Median ± IQR	368.5 ± 371.0	374 ± 433.8	>.05

Abbreviations: AD, Atopic Dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI75, EASI score improvement of at least 75%; IGA, Investigator's Global Assessment; IQR, Interquartile Range; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; SCORAD, SCORing Atopic Dermatitis.

[a]Compared with Wilcoxon's matched pairs tests and Student's *t* test.

[b]Performed in 112 patients.

[c]Performed in 114 patients.

For the median ± IQR total blood oeosinophil count (measured in 114 patients), no significant differences from baseline were found by week 16 (368.5 cell/mm^3 ± 371.0 vs 374 cell/mm^3 ± 433.8; $P > .05$) (Table 2).

3.2 | Perennial allergic rhinoconjunctivitis (PAR) and perennial allergic asthma (PAA)

In our patients, the diagnosis and assessment of severity of allergic asthma was made on the basis of a history of variable respiratory symptoms, skin prick test results and evidence of variable expiratory airflow limitation. Clinical history, ENT and skin prick tests were used for the diagnosis of allergic rhinitis. Fifty (40.1%) patients were identified as having PAR and/or PAA caused by allergens that are present year-round (22 women; 28 men; median ± IQR age: 37 ± 17 years).

In 41 patients with PAR (Figure 1), the median ± IQR RCSS global total score significantly decreased from 28.0 ± 10.0 at baseline to 18.0 ± 8.0 at 16 weeks ($P < .001$). In the PAR subgroup, at 16 weeks, the median ± IQR RQLQ score significantly improved from 2.5 ± 1.5 at baseline to 1.3 ± 1.2 ($P < .001$). The minimally clinically meaningful difference of 0.5 points or more was observed in 30 out of 41 patients (73.2%).

In 32 patients with PAA (Figure 2), the median ± IQR FEV1 before bronchodilation was 3.5 L ± 0.60 at baseline and 3.5 L ± 0.64 at week 16 ($P > .05$), while the median ± IQR FEV1 (per cent of predicted value before broncodilation) was 91.5 ± 15.0 at baseline and 91.4 ± 18.6 at week 16 ($P > .05$). Our results showed no significant differences in the median values for FEV1 before broncodilation. At the end of the treatment period, 15 patients improved to 0.1 L or more and 10 patients to more than 0.2 L.

At week 16, the median ± IQR ACT score significantly increased from 22.5 ± 5.8 to 24.0 ± 2.8 ($P < .001$). Thirteen of 32 patients (40.6%) achieved the minimally clinically meaningful difference (at least three points) at the 16-week stage. At baseline, 21 of 32 patients (65.6%) had conditions that were considered as being under control; 31 of 32 patients (96.9%) had controlled asthma at week 16.

The median ± IQR ACQ-5 score significantly improved from 1.0 ± 1.9 at baseline to 0.4 ± 0.7 at 16 weeks ($P < .001$). The minimally clinically meaningful difference of 0.5 points or more was observed in 19 of 32 patients (59.4%).

The median ± IQR AQLQ score significantly increased from 5.8 ± 2.5 at baseline to 6.5 ± 0.7 at 16 weeks ($P < .001$). Twenty-two of 32 patients (68.8%) achieved the minimally clinically meaningful difference (at least 0.5 points) in the AQLQ. At baseline, a total of

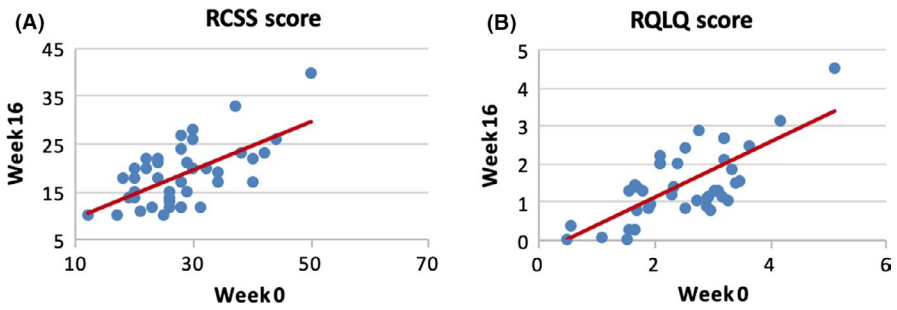


FIGURE 1 Summary of efficacy outcomes in the subgroup of patients with perennial allergic rhinitis at week 16 (n = 41) measured by RCSS score (A) and RQLQ score (B). RCSS, Rhinitis Control Scoring System; RQLQ, Rhinitis Quality of Life Questionnaire

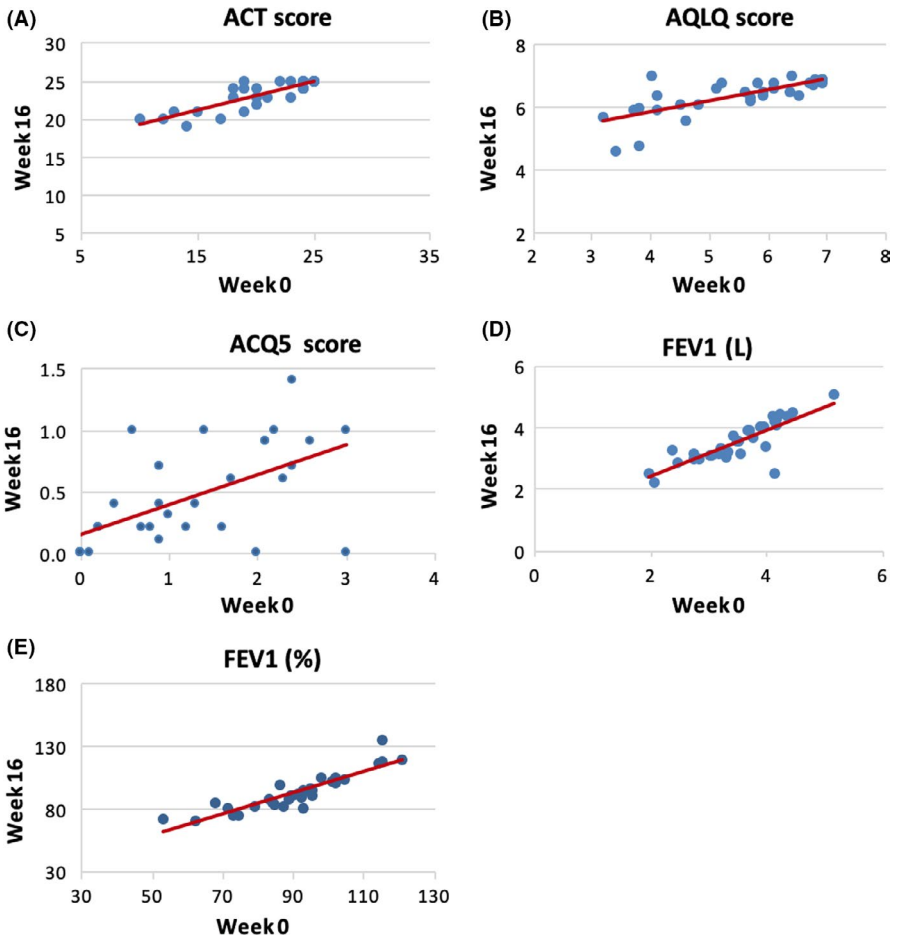


FIGURE 2 Summary of efficacy outcomes in the subgroup of patients with perennial allergic asthma at week 16 (n = 32) measured by ACT score (A), AQLQ score (B), ACQ5 score (C), FEV1(L) (D) and FEV1(%) (E). ACQ-5, Asthma Control Questionnaire (5 items); ACT, Asthma Control Test; AQLQ(S), Asthma Quality of Life Questionnaire (standardized version); FEV1, Forced Expiratory Volume in 1 s

nine patients (28.1%) had developed at least one severe exacerbation requiring the initiation of systemic corticosteroids during the four months running up to the dupilumab treatment.

Only one of 32 (3.1%) patients developed at least one severe exacerbation during the treatment period ($P < .05$).

3.3 | Safety

The overall incidence of adverse events (AEs) during the 16-week treatment phase was 31.7%, with the most common AEs being conjunctivitis, arthralgia and injection site reaction (see Table 3). Thirty-five patients (28.5%) developed de novo conjunctivitis during dupilumab therapy.

Reported dupilumab-associated conjunctivitis was mild in 22 patients (62.8%), moderate in 10 (28.6%) and severe in three (8.6%). In 23 cases (65.7%), conjunctivitis was recovered/resolved or recovering/resolving by the end of week 16. Eleven cases (31.4%) were not recovered/resolved by that time, and one case (2.9%) was recovered/resolved with sequelae. Dupilumab treatment was discontinued for one patient who developed bilateral conjunctivitis and cicatricial ectropion.[19]

As previously described, cases were managed with topical therapies, for example tear substitutes, topical steroids, topical vasoconstrictors, anti-histamines, mast cell stabilizers, eye drops containing cyclosporine and topical antibiotics.[20-24] No treatment-emergent AEs were reported during the study.

TABLE 3 Summary of adverse events (AEs) reported during the 16-week treatment period

AEs, n (%)	N = 123
Overall	39 (31.7)
Conjunctivitis	35 (28.5)
Arthralgia	3 (2.4)
Injection site reaction	3 (2.4)
Orofacial HSV reactivation	2 (2.2)
Headache	1 (1.6)
Any AE leading to discontinuation of study	1 (1.6)

Abbreviation: HSV, Herpes simplex virus.

4 | DISCUSSION

This is the first observational study that demonstrates the effectiveness of dupilumab in real-life conditions in patients with PAR and/or PAA associated with msAD.

The performance of new AD treatments to date has been demonstrated primarily in clinical trial settings[25-27] rather than in real-life studies.[20,28-34] Given the indicators that suggest the use of dupilumab to treat AD, we must now also study the associated atopic comorbidities. Indeed, the European Medicines Agency recently approved the use of dupilumab to treat bronchial asthma Th2 inflammation in patients over 12 years of age, given the failure of CSI/LABA/LAMA as an add-on therapy. The initial dosage of 600 mg was followed by 300 mg doses administered every two weeks, in cases where there was an associated comorbidity with a patient's msAD. It is of fundamental importance to remember that atopic dermatitis is a systemic pathology and that it is therefore important to contextually assess the associated atopic comorbidities, as was done in this study.

In our study, after 16 weeks of treatment, dupilumab significantly improved all AD objective and subjective scores and QoL index.

Although our results include fewer subjects and patients with initial EASI score values of 24 or higher, they are in accordance with previous results phase 3 clinical trial results which show that dupilumab effectively reduced the signs and symptoms of msAD in adults.[25-27]

Patients in our study were asked to discontinue systemic immunosuppressants before beginning dupilumab treatment. However, concomitant treatment with OCS continued in only three patients, using a tapering schedule to keep the disease under control before attaining good efficacy with dupilumab. Interestingly, a remarkable number of patients (87.5%) were able to discontinue this medication. OCS use is highly prevalent, and the fact that these drugs can affect the onset of complications, from minor events to potentially life-threatening conditions, is a well-known issue impacting patients' QoL.[35]

Our patients also experienced a significant decrease in serum IgE at follow-up, in line with previous studies.[28,29,33,34] The decrease in IgE serum levels under dupilumab may be interpreted as a marker of IL-4/IL-13 blockade, since these cytokines cause increased production of IgE by B cells.[12]

For our cohort of patients, oeosinophil count did not change significantly between baseline and week 16 follow-up, counter to previously reported data from clinical trials.[25-27] Nevertheless, in the CAFE trial and in the SOLO1 and SOLO2 trials, dupilumab-treated patients had a greater mean initial increase from baseline in oeosinophil count compared to subjects treated with a placebo, with subsequent decreases towards or below baseline levels by week 16.[25,26] The increase in the blood oeosinophil counts might be explained by the a dupilumab mechanism that blocks the migration of oeosinophils into tissue by inhibiting interleukin-4- and interleukin-13-mediated production of eotaxins but does not block oeosinophil production in bone marrow.[28,36] This action results in a transient increase in circulating oeosinophil counts. The findings of these studies differed from those in another real-life study, in which the proportion of dupilumab-treated patients who had oeosinophilia within 6 months of follow-up (57.0%) was significantly higher than the proportion at baseline (33.7%).[28] It is possible to hypothesize that patients already had higher oeosinophil levels at the start since mostly severe patients were included in this study.

Furthermore, our study evaluated the efficacy of dupilumab in a subgroup of patients with msAD and comorbid PAR or PAA. AD is often associated with other atopic diseases, such as allergic rhinitis and allergic asthma, and may occur as part of the atopic march

mentioned above.[7] Our real-life study data on the outcomes for dupilumab treatment in patients with concomitant PAR or PAA are unique. In the current study, dupilumab treatment in patients with comorbid PAR was associated with significant improvements in several patient-reported outcomes, including PAR disease control as measured by an RCSS global score and PAR QoL as assessed by validated, disease-specific tools (RQLQ).

In addition, our study showed that dupilumab significantly improved comorbid PAA control, as assessed by the ACT and ACQ-5 scores, and by disease-related QoL measured using AQLQ(S) scores. Moreover, there was a clinically relevant improvement in FEV1 (≥0.1 L) in almost half of the patients. It is worth highlighting that only one patient developed at least one severe exacerbation during the treatment period.

These findings are in line with the significant improvements that have been observed in co-existing asthma in a subgroup of AD patients that was treated with dupilumab at week 16 of the CAFE, SOLO1 and SOLO2, and CHRONOS trials.[37] In these trials, an ACQ-5 improvement of 0.5 points or higher at week 16 was achieved by 31.6%, of the patients who received dupilumab, as compared to only 21.9% of patients who had received a placebo ($P < .05$ vs placebo). Another trial showed that, at week 16, adolescent patients with moderate-to-severe inadequately controlled AD and comorbid asthma or allergic rhinitis had numerically greater improvement in asthma control (measured by least-squares mean changes from baseline in the Juniper Asthma Control Questionnaire) and numerically greater reduction in symptoms of allergic rhinitis (measured by least-squares mean changes from baseline in the Total Nasal Symptom Score) with dupilumab vs placebo.[38] In a real-life study, only four of 15 dupilumab-treated patients with msAD and allergic rhinitis or rhinosinusitis showed improvement based on ENT examinations at week 16.[34] In addition, this study showed significant decreases in fractional exhaled nitric oxide (FeNO), a marker of oeosinophilic airway inflammation, and no significant changes in ACT and spirometry at week 16 in any patient with msAD and asthma (n = 15) who had been treated with dupilumab.[34]

The results of our study are consistent with those observed in a clinical trial in which dupilumab was used as add-on therapy alongside medium-to-high-dose inhaled corticosteroids and long-acting β2-agonists. That study showed simultaneous improvement in lung function (FEV1), reduced the rate of severe exacerbations and significantly improved the allergic rhinitis-associated nasal symptoms at week 24 in patients with uncontrolled persistent asthma and comorbid PAR.[13]

Although the treatment is generally well tolerated, there have been reports of high rates of conjunctivitis in AD patients taking dupilumab. The reported incidence in clinical trials[25-27] and in real-life studies[20,28-33] ranges from 4.7% to 28%, and from 8.6% to 62% of dupilumab-treated patients, respectively. Dupilumab-associated conjunctivitis was reported in 28.5% of the patients undergoing treatment in our study. Predictors of its incidence are not well understood. In previous studies, severe AD,[21,22,26] prior history of conjunctivitis,[21,26] atopic AD phenotype,[22,26] and high baseline IgE levels and oeosinophil counts[21] have been suggested as risk factors for dupilumab-associated conjunctivitis. Patients with AD have a greater prevalence of ocular comorbidities than the general population,[39] but no association has been shown between administering dupilumab for asthma or nasal polyposis and higher rates of conjunctivitis.[22] Some authors hypothesize that both dupilumab- and AD-related mechanisms may be involved and that ocular or immune differences between patients with AD and other type 2 diseases might be relevant factors.[21]

The limitations of this study include a fast follow-up time and a lack of control patients. Another limitation is the relatively small population studied with PAR and/or PAA, but the estimated sample size was powered to show statistically significant differences from baseline.

In conclusion, this is the first prospective real-life study of a successful treatment of PAR and/or PAA (both in terms of symptoms and QoL) associated with msAD with an anti-IL-4Rα drug in a patient population aged 18 years and over. A limitation of this study is the relatively small sample size. Future studies are required to investigate the benefit of dupilumab in this subgroup of patients with concomitant AD and allergic respiratory diseases.

This 16-week study involved AD patients with inadequate response to/intolerance of CsA, or who had been medically classified as unsuitable for CsA treatment. In this group, dupilumab significantly improved AD and QoL, reducing the need for concomitant OCS. Our data showed an effectiveness comparable to phase 3 clinical trials but also a higher incidence of conjunctivitis. These results validate the key role that IL-4 and IL-13 play in the induction and perpetuation of type 2 immune responses implicated in AD and atopic comorbidities.

CONFLICT OF INTEREST

All Authors claim to have no conflicts of interest except Giorgio W. Canonica who received research grants as well as lecture or advisory board fees from A. Menarini, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, Glaxo Smith Kline, Mundipharma, Novartis, Sanofi-Aventis, Teva.

AUTHOR CONTRIBUTIONS

EN, VP, CL, AD, LM, EDL, MC and LB were nothing to disclose. Dr Canonica reports grants, personal fees and other from A. Menarini, grants, personal fees and other from AstraZeneca, grants, personal fees and other from Boehringer Ingelheim, grants, personal fees and other from Chiesi Farmaceutici, grants, personal fees and other from Genentech, grants, personal fees and other from Guidotti-Malesci, grants, personal fees and other from Glaxo Smith Kline, grants, personal fees and other from Mundipharma, grants, personal fees and other from Novartis, grants, personal fees and other from Sanofi-Aventis, grants, personal fees and other from Teva, outside the submitted work.

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How to cite this article: Nettis E, Patella V, Lombardo C, et al. Efficacy of dupilumab in atopic comorbidities associated with moderate-to-severe adult atopic dermatitis. *Allergy*. 2020;75:2653–2661. https://doi.org/10.1111/all.14338

APPENDIX 1

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