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Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort

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Abstract

Background: Dupilumab is the first biologic available to treat atopic dermatitis (AD). Its effectiveness and safety were demonstrated in clinical trials.

Objective: We sought to assess the effectiveness and safety of dupilumab in adults with AD in a real-life French multicenter retrospective cohort.

Methods: Patients were included between March 2017 and April 2018. Efficacy outcomes were collected both at baseline and three months (M3), when available, including SCORAD (Scoring Atopic Dermatitis) and EASI (Eczema Area and Severity Index) scores. Adverse events (AE) were recorded at the follow-up.

Results: We included 241 patients. The median follow-up time was 3.8 ± 3.7 months. SCORAD₇₅ and EASI₇₅ were achieved in 27/163 (16.6%) and 40/82 (48.8%) patients, respectively. The median SCORAD and EASI at M3 were significantly lower compared with baseline (25 ± 21 vs 56 ± 27.4 , $p < 10^{-9}$ and 4.1 ± 6.8 vs 17.9 ± 15.4 , $p < 10^{-9}$, respectively). Conjunctivitis was reported in 84/241 (38.2%) patients. The proportion of eosinophilia ($>500/\text{mm}^3$) during follow-up (57%) was higher than at baseline (33.7%) ($n=172$, $p < 10^{-6}$). Dupilumab was stopped in 42 cases, 27 of which were due to an AE.

Limitations: No control group, missing data.

Conclusion: This real-life study demonstrated results similar to clinical trials, with regard to dupilumab effectiveness, but revealed a higher frequency of conjunctivitis and eosinophilia.

Body of manuscript:**Introduction**

Atopic dermatitis (AD), a chronic inflammatory disease affecting 2-5% of adults (1), may have a major impact on the quality of life. For moderate-to-severe AD, the efficiency of topical therapy is often limited, and conventional systemic treatments may be required (e.g., cyclosporine) which may carry significant risks for long-term use. Dupilumab, a monoclonal antibody directed against the alpha subunit of the interleukin (IL)-4 receptor, is the first biologic available for the treatment of inadequately controlled moderate-to-severe AD in adults. The data available in terms of efficacy and safety are from clinical trials (2-4) and therefore represent a select population that does not necessarily reflect prescribing conditions in daily practice. This study was designed to assess the effectiveness and the tolerance of dupilumab in adult patients with AD from a real-life French multicenter retrospective cohort.

Methods

Study design and population

This study evaluated data collected from a French multicenter retrospective cohort conducted by the Groupe de Recherche sur l'Eczema Atopique (GREAT). All consecutive patients >18 years old, diagnosed with AD, according to the revised Hanifin and Rajka criteria (5), and evaluated by members of the GREAT group from March 2017 to April 2018 were eligible for this study. The patients received dupilumab for moderate-to-severe AD due to inefficiency, loss of efficiency or contraindication of a previous systemic agent according to the French early access program set up during this period.

This study was approved by the ethical organization "Commission Nationale de l'Informatique et des Libertés" (CNIL #DEC16-355). Patients' nonopposition for the use of their nonidentified record data was obtained for this noninterventional study, according to French legislation.

Data collection

A questionnaire was completed by clinicians from the medical charts. Baseline characteristics were demographic variables, comorbidities, AD form, previous treatments, date of introduction and dose of dupilumab. Three validated scores, (i) SCORAD (Scoring Atopic Dermatitis), (ii) EASI (Eczema Area and Severity Index), (iii) DLQI (Quality of Life Index) (6-8) and the blood eosinophil (B-eos) count were recorded at baseline and during the follow-up. In addition, adverse events (AEs) were collected. Finally, we evaluated the discontinuation of dupilumab at the end of the follow-up and collected the reasons for stopping treatment.

Outcomes

SCORAD, EASI and DLQI at three months (M3) were defined by the highest score – from a conservative approach – recorded after either two, three or four months of treatment in order to increase the number of patients with available outcomes, because the follow-up time was

not standardized among the different centers. The primary outcome was defined as SCORAD at M3 compared with baseline. The secondary outcomes were defined in the same way for EASI and DLQI scores. Other outcomes for effectiveness were (from baseline to M3) the median percent change of SCORAD and EASI, the mean change of DLQI, and the proportion of patients with an improvement on the SCORAD or EASI of at least 50% or 75% (SCORAD50, SCORAD75, EASI50, EASI75). AD flares were defined as AD exacerbations according to the investigators' opinion. Eosinophilia and hypereosinophilia were defined as B-eos >500 and >1500 cells/mm³, respectively. Eosinophilia in follow-up (at least one dosage within 6 months of follow-up) was compared with baseline. AEs were defined as occurrences of any untoward medical condition during the treatment period.

Statistical analyses

Characteristics of patients with and without an assessment of outcomes were compared using Student's t-tests, or Wilcoxon tests in cases of nonnormality for quantitative variables, and Fisher's exact tests for qualitative variables. The comparison between the SCORAD (and EASI and DLQI scores) from baseline to M3 was performed using Wilcoxon matched pairs tests. A sensitivity analysis was performed by excluding the patients treated with concomitant systemic treatments for AD. The comparison between the proportion of eosinophilia from baseline to follow-up was performed using McNemar's test. AEs were reported using number (percentage), as well as reasons for stopping dupilumab. Because the follow-up was not the same for all patients, we evaluated survival of dupilumab during the follow-up using the Kaplan-Meier method. All statistical analyses were performed using R software, version 3.3.3, using the "Hmisc" and "survival" packages. The threshold for statistical significance was set at $p < 0.05$.

Results

Baseline characteristics

The study population included 241 patients from 29 hospital centers, with a median follow-up time of 3.8 ± 3.7 months (**Table 1**). The median scores at baseline were 54 ± 26.8 for SCORAD, 18.3 ± 15 for EASI and 14 ± 10.8 for DLQI. The SCORAD score was assessed at baseline and M3 in 163 (67.6%) patients. Complete data was available for 82 (34%) patients for EASI and 85 (35.3%) for DLQI.

Dupilumab effectiveness

Median SCORAD at M3 was significantly lower compared with baseline (25 ± 21 vs 56 ± 27.4 , $p < 10^{-9}$), corresponding to a median percent change of -52.5 ± 44 (**Table 2**) (**Figure 1**). The median EASI and DLQI at M3 were significantly lower compared with baseline (4.1 ± 6.8 vs 17.9 ± 15.4 , $p < 10^{-9}$ and 4 ± 8 vs 13 ± 11 , $p < 10^{-9}$, respectively). A total of 188 (79%) patients were concomitantly treated with topical corticosteroids.

The results were similar when we excluded the 12 patients treated with concomitant systemic treatments (**data not shown**).

At M3, 86/163 (52.8%) patients had achieved SCORAD50, and 27 (16.6%) SCORAD75, while 59/82 (72%) patients had achieved EASI50 and 40 (48.8%) EASI75 (**Table 2**). Patients who achieved SCORAD50 at M3 had a higher SCORAD at baseline compared with their counterparts (62 ± 24 vs 48 ± 22.8 , $p < 0.001$) and a lower proportion of topical corticosteroids (TCS) use concomitantly with dupilumab (69.4% vs 87%, $p < 0.008$) (**data not shown**).

AD flares

While being treated with dupilumab, 75 (31.1%) patients experienced at least one event considered as an AD flare by the investigator. A total of 106 flares were recorded. When information on severity of flares was available ($n=96/106$), 20 (20.8%) flares were described as severe exacerbation of AD. The first exacerbation occurred at a median of 2.3 ± 1.5 months after dupilumab introduction. The management of flares was mainly accomplished by

the use of topical treatments (emollients, TCS or tacrolimus) (89.4%). In one patient, concomitant treatment with methotrexate was initiated.

Dupilumab safety

At least one AE was reported in 171 of 241 (71%) patients, (**Table 3**). Of 220 patients, (48.6%) had a noninfectious ophthalmological AE, including 84 (38.2%) cases of conjunctivitis. Among the 84 patients with conjunctivitis diagnosed by the investigator, 39 were referred to an ophthalmologist who made the diagnosis of conjunctivitis in 32 (82.1%) patients. The development of conjunctivitis was associated with a medical history of allergic conjunctivitis (57.3 vs 35.7%, $p<0.003$).

Six of 208 (2.9%) patients developed an eye infection, including one patient with HSV keratoconjunctivitis.

Of the 177 patients who had at least one B-eos count within 6 months of follow-up, 100 (56.5%) had blood eosinophilia. When data were available (172/177), the proportion of patients who had eosinophilia during the follow-up (57%) was significantly higher than at baseline (33.7%) ($p<10^{-6}$). The result of the B-eos count in the follow-up was unknown for six patients. Among the 94 patients with eosinophilia, 28 (29.8%) had hypereosinophilia (>1500 cells/mm³), with a maximum of 7800/mm³. Eosinophilia during the follow-up was associated with eosinophilia at baseline (64.2% vs 13.5%, $p<10^{-9}$), asthma (81.4% vs 49.3%, $p<0.001$), allergic rhinitis (67.8% vs 50%, $p=0.025$), and food allergy (29.7% vs 16%, $p=0.044$). No clinical impact was reported.

A primary cutaneous CD30+ lymphoma was diagnosed in one patient in whom AD was treated with dupilumab for three months. However, a relation between exposure to dupilumab and the development of this lymphoma was not established.

Discontinuation of dupilumab

132 The proportion of patients still treated with dupilumab at 3 and 6 months was 95.6%
133 [92.9:98.5] and 79.7% [73.2:86.8], respectively. The reasons for stopping dupilumab
134 treatment in 42 patients are summarized in **Table 4**.

Discussion

This observational study demonstrates the effectiveness of dupilumab in real-life conditions and provides safety data during the first 6 months of exposure to dupilumab.

The strengths of this real-life study are that patients were not selected as in clinical trials and represented a large sample of the total population treated with dupilumab in France (estimated at 530 patients in April 2018). However, our study has some limitations, the main one being the absence of a control group. Other factors such as the natural evolution of the disease and regression towards the average, may have had an impact on outcomes of efficacy and safety. Another important limit was the retrospective study design, leading to a significant rate of missing data concerning outcomes, leading us to consider the maximum score at two to four months for the definition of the outcome in order to increase the number of patients with available outcomes. However, the median SCORAD according to this definition (25 ± 21 , $n=163$) was similar to the median SCORAD calculated exclusively at three months (25.7 ± 22 , $n=117$), suggesting a limited measurement bias. In addition, with regard to efficacy, patient characteristics with or without available scores were similar, suggesting that the selection bias of patients was limited. Moreover, the “real-life” setting of this study conducted to evaluate the efficiency of dupilumab associated in most of patients with a concomitant use of TCS. Concerning safety outcomes, we may have underestimated the proportion of AEs and the definition of AEs as flares and conjunctivitis were subject to investigator assessment and not standardized. Finally, we were not able to assess the evolution of B-eos count because only a single dosage was available for most of the patients.

Characteristics of our 241 patients were similar to those of patients included in clinical trials in terms of age, sex ratio, disease duration, atopic comorbidities and severity (2–4). Prior to dupilumab, our patients may have received more previous systemic treatments (median of approximately 3 previous lines), including cyclosporine, as in the LIBERTY AD CAFÉ study (4), or methotrexate (9).

Our study confirmed the effectiveness of dupilumab in real-life conditions, with results similar to those obtained in clinical trials. The median percent changes in SCORAD and EASI at M3 were -52.5% and -71.3%, respectively in our study vs the least-squares mean percent change at week 16 in trials of -57.7% and -72.3% (SOLO1), -51.1% and -67.1% (SOLO2), -62.1% and -76.7% (CHRONOS), and -62.4% and -79.8% (CAFÉ). EASI75 was achieved at M3 in 48.8% of our patients vs at week 16 in the trials, 51% (SOLO1), 44% (SOLO2), 69% (CHRONOS), and 62.6% (CAFÉ) (2-4).

For 12 patients, dupilumab was administered with another systemic agent during the follow-up (mainly cyclosporine or methotrexate). For most of these patients, this concomitant treatment corresponded to an overlap between the systemic agent previously prescribed and the introduction of dupilumab, to keep the disease controlled before obtaining good efficacy with dupilumab. The sensitivity analysis performed after exclusion of these patients led to similar efficacy results. Results from the CHRONOS trial suggested that dupilumab efficacy was higher when combined with TCS (3). In our population, 79% received a concomitant treatment with TCS. The patients who did not achieve SCORAD50 at M3 used slightly more TCS concomitantly with dupilumab than those who reached SCORAD50, suggesting the need for TCS to control the disease in our study.

Compared to the results from clinical trials, we observed a particularly high rate of conjunctivitis with dupilumab. Indeed, this AE was reported in 38.2% of our patients vs 8% of patients receiving dupilumab in a meta-analysis based on trials (10). When the patient was referred to the ophthalmologist, the diagnosis of conjunctivitis was confirmed in more than 80%, suggesting a slight overestimation of this proportion. Most of the conjunctivitis was not viral or bacterial and remained of unknown cause. This AE seems to be specific to AD since it was not observed in patients involved in trials assessing dupilumab in conjunction with asthma (11,12) and nasal polyposis (13). The occurrence or recurrence of conjunctivitis with dupilumab treatment was significantly associated with a past medical history of atopic conjunctivitis in our study, while this AE was also associated with other atopic comorbidities

and with AD severity in a series of 12 patients (14). The semiology and pathophysiology of dupilumab-induced eye disorders remain unknown and future studies are needed to better explain the mechanism and the specificity of this AE. In our study, several therapeutics were prescribed, from artificial tears to cyclosporine eye drops, without available data concerning their effectiveness. No severe complications were reported by our investigators; however, ophthalmological AEs often have an impact on quality of life and can lead to treatment discontinuation.

The other AE of interest in our study was eosinophilia. Indeed, we observed a higher proportion of eosinophilia from baseline to follow-up as well as the occurrence of hypereosinophilia in 23 patients. This AE appeared more frequently in our study than in the AD trials. Indeed, the clinical trials showed transient eosinophilia in less than 2% of patients (2,3). In trials assessing dupilumab in asthma, a transient increase of B-eos was reported mostly in patients with pre-existing eosinophilia at baseline (11,12). In our study, eosinophilia with dupilumab was also associated with a history of eosinophilia, asthma and allergic rhinitis. None of our patients presented clinical signs of organ involvement due to eosinophil infiltration. However, our investigators decided to stop dupilumab for five patients because of persistent hypereosinophilia without other etiology than dupilumab. The mechanisms underlying dupilumab-induced hypereosinophilia remain unknown. Some researchers raised the hypothesis that dupilumab blocks the migration of eosinophils into tissue by inhibiting the interleukin-4– and interleukin-13–mediated production of eotaxins and vascular cell adhesion molecule but not eosinophil production from bone marrow (15). Further investigations are necessary to assess whether this dupilumab-increased eosinophilia may have a clinical impact or not.

In conclusion, this real-life study of dupilumab in the treatment of AD in adults showed similar effectiveness results as those observed in clinical trials but showed a higher frequency of conjunctivitis and eosinophilia, which can call into question the continuation of treatment.

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References:

1. Barbarot S , Auziere S , Gadkari A et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy*. 2018;73(6):1284-1293.
2. Simpson EL, Bieber T, Guttman-Yassky et al. Two Phase 3 Trials of Dupilumab versus Placebo in AD. *N Engl J Med*. 2016;375(24):2335-2348.
3. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe AD with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet Lond Engl*. 2017;389(10086):2287-303.
4. De Bruin-Weller M, Thaçi D, Smith C h., et al. Dupilumab with concomitant topical corticosteroids in adult patients with AD who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY AD CAFÉ). *Br J Dermatol*. 2018;178(5):1083-11015.
5. Hanifin JM, Cooper KD, Ho VC, Kang S, Krafchik BR, Margolis DJ, et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines". *Journal of the American Academy of Dermatology*. 2004;50:391-404
6. Severity scoring of AD: the SCORAD index. Consensus Report of the European Task Force on AD. *Dermatol Basel Switz*. 1993;186(1):23-31.
7. Hanifin JM, Thurston M, Omoto M et al. . The eczema area and severity index (EASI): assessment of reliability in AD. EASI Evaluator Group. *Exp Dermatol*. 2001;10(1):11-8.
8. Lundberg L, Johannesson M, Silverdahl M et al. . Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. *Br J Dermatol*. 1999;141(6):1067-75.
9. Goujon C, Viguier M, Staumont-Sallé Det al. Methotrexate Versus Cyclosporine in Adults with Moderate-to-Severe AD: A Phase III Randomized Noninferiority Trial. *J Allergy Clin Immunol Pract*. 2018;6(2):562-569.
10. Ou Z, Chen C, Chen A et al.. Adverse events of Dupilumab in adults with moderate-to-severe AD: A meta-analysis. *Int Immunopharmacol*. 2018;54:303-10.
11. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *The Lancet*. 2016;388(10039):31-44.
12. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455-66.
13. Bachert C, Mannent L, Naclerio RM, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. *JAMA*. 2016;315(5):469-79.13.

- 257 14. Treister AD , Kraff-Cooper C , Lio PA. Risk Factors for dupilumab-associated
258 conjunctivitis in patients with atopic dermatitis. JAMA Dermatol. 2018 Aug 29. doi:
259 10.1001/jamadermatol.2018.2690. [Epub ahead of print]
- 260 15. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-
261 Dependent Severe Asthma. N Engl J Med. 2018;378(26):2475-85.

Table legends

Table 1. Baseline characteristics of the whole population and comparison of patients with and without an assessment of the SCORAD score at baseline and three months

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Table 3. Adverse events

Table 4. Discontinuation of dupilumab at the end of the follow-up period

Figure legend

Figure 1. "SCORAD, EASI and DLQI scores at baseline and at month 3."

Table 1. Baseline characteristics of the whole population and comparison of patients with and without an assessment of the SCORAD score at baseline and three months.

	N (N SCORAD assessed)	Whole population (n=241)	Assessment of the SCORAD score at baseline and three months		
			Yes (n=163)	No (n=78)	p
Demographical variables					
Follow-up (months) *	241 (78)	3.8 (3.7)	4.3 (3.9)	3.3 (3.6)	< 0.001
Age (years) *	241 (78)	37 ± 22	36 ± 23	38 ± 19.5	0.27
Male gender	240 (162)	144 (60)	98 (60.5)	46 (59)	0.89
Body mass index (kg/m²)	197 (53)	24.4 ± 4.7	24.5 ± 4.6	24.2 ± 5.2	0.71
Educational level					0.56
Less than 9 years of full-time education	178 (132)	1 (0.6)	1 (0.8)	0 (0)	
9 years of full-time education	178 (132)	14 (7.9)	9 (6.8)	5 (10.9)	
Less than 11 years of full-time education	178 (132)	27 (15.2)	21 (15.9)	6 (13)	
12 years of full-time education	178 (132)	46 (25.8)	31 (23.5)	15 (32.6)	
More than 12 years of full-time education	178 (132)	90 (50.6)	70 (53)	20 (43.5)	
Smoking status					0.11
Current smoker	204 (145)	64 (31.4)	40 (27.6)	24 (40.7)	
Former smoker	204 (145)	38 (18.6)	26 (17.9)	12 (20.3)	
Never smoker	204 (145)	102 (50)	79 (54.5)	23 (39)	
Alcohol > 20 g/day	195 (141)	11 (5.6)	8 (5.7)	3 (5.6)	> 0.99
Atopic dermatitis					
Diagnosis					0.54
Infant	237 (160)	81 (34.2)	59 (36.9)	22 (28.6)	
Child	237 (160)	118 (49.8)	78 (48.8)	40 (52)	
Teenager	237 (160)	18 (7.6)	11 (6.9)	7 (9.1)	
Adult	237 (160)	20 (8.4)	12 (7.5)	8 (10.4)	
Localisation					
Diffuse	230 (157)	207 (90)	144 (91.7)	63 (86.3)	0.24
Head and neck	225 (155)	18 (8)	11 (7.1)	7 (10)	0.44
Scores at baseline					
SCORAD *	211 (48)	54 ± 26.8	56 ± 27.4	48.5 ± 29.3	0.017
EASI *	100 (19)	18.3 ± 15	18.2 ± 15.3	20 ± 11.4	0.32
DLQI *	122 (19)	14 ± 10.8	14 ± 10.5	14 ± 8.5	0.30
History of treatments for atopic dermatitis					
Topical treatments					
Topical corticosteroids	235 (159)	232 (98.7)	157 (98.7)	75 (98.7)	> 0.99
Topical tacrolimus	218 (150)	179 (82.1)	120 (80)	59 (86.8)	0.26
Emollients	237 (160)	236 (99.6)	159	77 (100)	> 0.99

(99.4)

Systemic treatments

Number of lines	241 (78)	2.9 ± 1.4	2.8 ± 1.4	3.2 ± 1.5	0.050
Phototherapy	236 (158)	154 (65.3)	98 (62)	56 (71.8)	0.15
Cyclosporine	239 (162)	179 (74.9)	115 (71)	64 (83.1)	0.06
Methotrexate	232 (157)	125 (53.9)	84 (53.5)	41 (54.7)	0.89
Azathioprine	219 (148)	24 (11)	14 (9.5)	10 (14.1)	0.36
Other systemic treatment ^a	221 (152)	75 (33.9)	48 (31.6)	27 (39.1)	0.29

Medical history

Atopy

Allergic asthma	235 (159)	155 (66)	103 (64.8)	52 (68.4)	0.66
Allergic rhinitis	226 (157)	129 (57.1)	98 (62.4)	31 (44.9)	0.019
Allergic conjunctivitis	225 (158)	101 (44.9)	74 (46.8)	27 (40.3)	0.38
Food allergy	224 (155)	58 (25.9)	41 (26.5)	17 (24.6)	0.87
Eosinophilia > 500 cells/mm ³	218 (150)	88 (40.4)	63 (42)	25 (36.8)	0.55

Viral infections

HSV recurrent-infection	198 (142)	26 (13.1)	19 (13.4)	7 (12.5)	> 0.99
Disseminated HSV infection	223 (156)	14 (6.3)	9 (5.8)	5 (7.5)	0.76
Varicella	159 (116)	30 (18.9)	23 (19.8)	7 (16.3)	0.82
Herpes zoster	204 (143)	11 (5.4)	8 (5.6)	3 (4.9)	> 0.99

N : number of patients with no-missing data; SCORAD: Scoring Atopic Dermatitis; EASI: Scores on the Eczema Area and Severity Index; DLQI: Dermatology Life Quality Index.

Quantitative variables are expressed as mean ± standard deviation and compared with Student t-tests, or median ± interquartile range and compared with Wilcoxon tests in case of non-normality (*). Qualitative variables are expressed as n (%) and compared with Fisher's exact tests.

^a Other systemic treatment: systemic corticosteroids (n=20), mycophenolate-mofetil (n=17), retinoids (n=16), omalizumab (n=12), polyvalent immunoglobulins (n=5), antifungals (n=3), tetracyclines (n=3), thalidomide (n=2), TNF alpha inhibitors (n=2), lebrikizumab (n=2), extra-corporal photopheresis (n=2), apremilast (n=1), dapsone (n=1), montelukast (n=1).

Table 2. Efficacy outcomes from baseline to three months.

Outcomes	N (% of the whole population)	Baseline	Month 3	p
SCORAD	163 (67.6)	56 ± 27.4	25 ± 21	< 10 ⁻⁹
EASI	82 (34.0)	17.9 ± 15.4	4.1 ± 6.8	< 10 ⁻⁹
DLQI	85 (35.3)	13 ± 11	4 ± 8	< 10 ⁻⁹
Median percent change ± IQR in SCORAD	163 (67.6)		-52.5 ± 44	
Median percent change ± IQR in EASI	82 (34.0)		-71.3 ± 41.3	
Mean change ± SE in DLQI	85 (35.3)		-7.3 ± 0.8	
SCORAD50	163 (67.6)		86 (52.8)	
SCORAD75	163 (67.6)		27 (16.6)	
EASI50	82 (34.0)		59 (72)	
EASI75	82 (34.0)		40 (48.8)	

N : number of patients with no-missing data; SCORAD: Scoring Atopic Dermatitis; EASI: Scores on the Eczema Area and Severity Index; DLQI: Dermatology Life Quality Index.

Scores are expressed as median ± interquartile range, and compared with Wilcoxon matched pairs tests.

The median percent change ± IQR was defined as the median of the percentage of change in SCORAD (or EASI score) from baseline to three months calculated for each patient. The mean change ± SE was defined as the mean of the difference of the DLQI score from baseline to three months calculated for each patient.

The proportion of patients with an improvement on the SCORAD or EASI of at least 50% or 75% from baseline to M3 (SCORAD50, SCORAD75, EASI50, EASI75) are expressed as n (%).

Table 3. Adverse events.

	N	Number of patients (%)
At least 1 adverse event	241	171 (71)
Non-infectious ophthalmological adverse event	220	107 (48.6)
Conjunctivitis		84 (38.2)
Ocular pruritus		52 (23.6)
Blepharitis		31 (14.1)
Xerophthalmia		27 (12.3)
Keratitis		14 (6.4)
Infectious ophthalmological adverse event	208	6 (2.9)
Conjunctivitis		4 (1.9)
Keratitis		2 (<1)
Hordeolum		1 (<1)
Eosinophilia (> 500 cells/mm³)^a	177	100 (56.5)
500-1000 cells/mm ³	94	44 (46.8)
1000-1500 cells/mm ³		22 (23.4)
> 1500 cells/mm ³		28 (29.8)
Injection-site reaction	229	21 (9.2)
HSV infection (off eye)	209	11 (5.3)
HSV disseminated-infection		1 (<1)
At least 1 other reported adverse event	241	60 (24.9)
Asthenia		7 (2.9)
Headaches		7 (2.9)
Diarrhea		4 (1.7)
Other cutaneous adverse events ^b		20 (8.2)
Other infectious adverse events ^c		12 (4.9)
Other adverse events ^d		24

N : number of patients with no-missing data; COPD: chronic obstructive pulmonary disease.

^a At least one dosage within 6 months of follow-up

^b Other cutaneous adverse events include : Folliculitis, peri-oral dermatitis, acne n=4 (1,7) ; Maculopapular rash n=3 (1,2) ; Flush n=3 (1,2) ; Bacterial cutaneous infection (impetigo, erysipelas, folliculitis) n=3 (1,2) ; Urticaria and angioedema n=2 (<1) ; Alopecia n=2 (<1) ; Erythema nodosum n=1 ; Photosensitivity n=1 ; Primary cutaneous CD30-positive lymphoma n=1.

^c Other infectious adverse events include : HPV infection n=4 (1,7) ; Upper respiratory tract infection n=3 (1,2) ; Urinary tract infection n=3 (1,2) ; Digestive infection (cholecystitis, sigmoiditis) n=2 (<1).

^d Other adverse events include : Nausea n=3 (1,2) ; Lymphadenopathy n=3 (1,2) ; Exacerbations asthma and COPD n=3 (1,2) ; Depressive syndrome n=3 (1,2) ; Chills n=2 (<1) ; Epigastric pain n=2 (<1) ; Weightloss n=1 ; Weight gain n=1 ; Dizziness n=1 ; Edema of the lower limbs n=1 ; Rectal bleeding n=1 ; Pudendal neuralgia n=1 ; Adrenal insufficiency n=1 ; Monocytosis n=1.

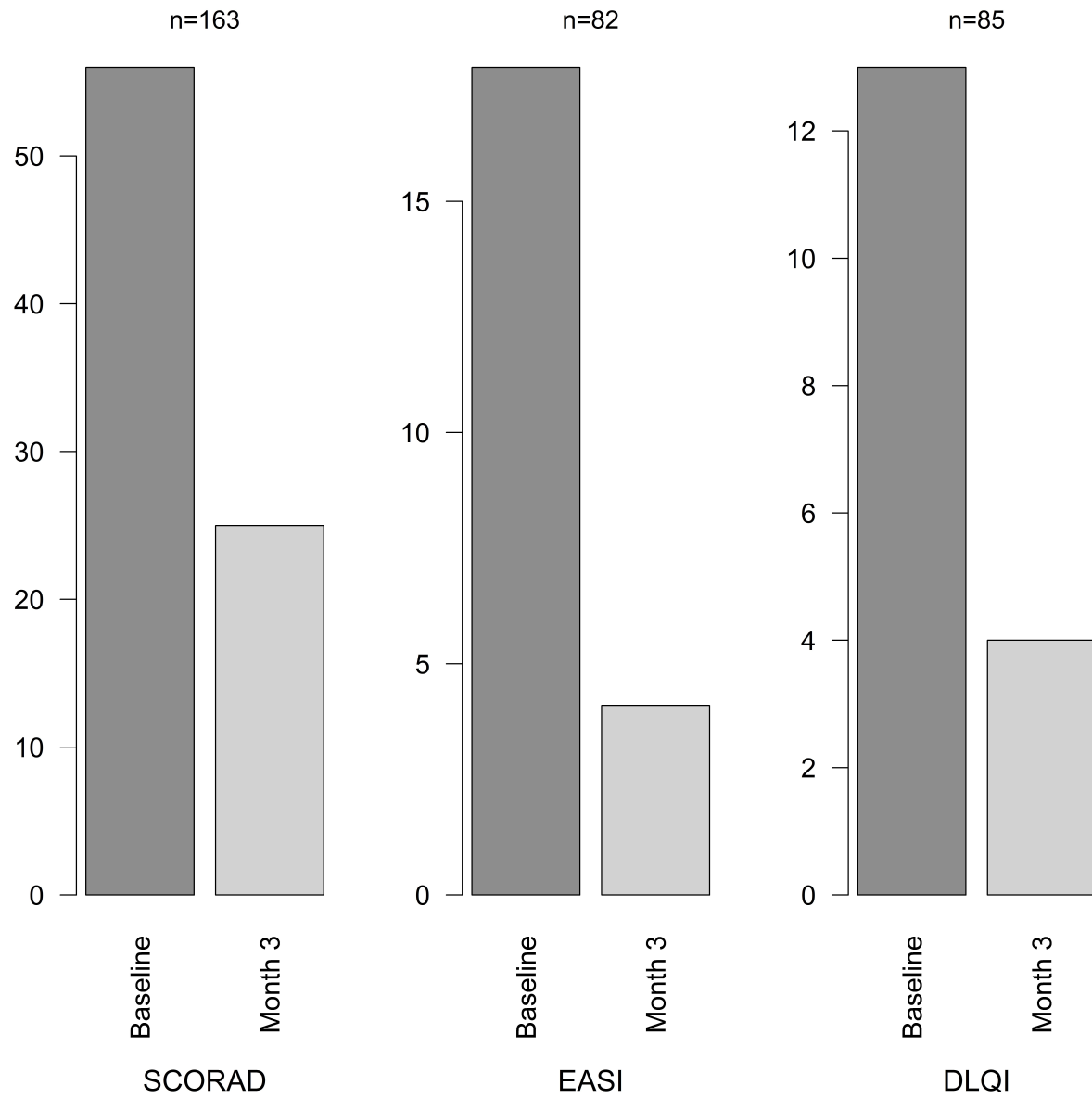
Table 4. Discontinuation of dupilumab at the end of follow-up.

	n (%)
Adverse event	27 (11,3)
Non-infectious ophthalmological adverse event	10 (4,2)
Persistent hypereosinophilia > 1500/mm ³	5 (2,1)
Another adverse event ^a	12 (5)
Inefficiency	9 (3,8)
Wish of the patient	8 (3,4)
Constraint of the visits	3 (1,3)
Constraint of the injections	2 (<1)
Another reason	3 (1,3)
Temporary contraindication	6 (2,5)
Wish of pregnancy	2 (<1)
Prevention of infectious risk before surgery	4 (1,7)
Improvement of atopic dermatitis	2 (<1)

Information concerning dupilumab discontinuation was not available for three patients.

Five patients had two reasons for stopping dupilumab, one patient had three reasons and one had four reasons.

^a Other adverse events: maculopapular rash (n=2), extension of molluscum contagiosum, urinary tract infection revealing pelvic fistula, alopecia, lymphadenopathies, exacerbation of COPD, exacerbation of asthma, primary CD30 + cutaneous lymphoma, lower limbs edema, nausea and diarrhea, hepatic cytolysis.



1 **Capsule summary:**

2 Few data are available with regard to the effectiveness and safety of dupilumab in real-life
3 conditions.

4 This study confirmed the effectiveness of dupilumab in daily practice but demonstrated a
5 higher frequency of conjunctivitis and eosinophilia compared with clinical trial results.