

## **Dupilumab in patients with atopic dermatitis – assessing treatment response, clinical features and potential biomarkers in real-life**

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### **Abstract**

**Background:** The clinical and pathophysiological heterogeneity of atopic dermatitis (AD) endophenotypes is associated with wide diversity in response to therapy. The aim of this study was to evaluate the response to dupilumab in a group of AD patients and identify clinical/immunological features associated with different patterns of response.

**Methods:** A retrospective observational study was performed, including 30 adults with AD who completed 12 months treatment with dupilumab, in a Portuguese Immunoallergology Department. Demographic, clinical, and immunological data were analyzed, including total serum IgE, sensitization to aeroallergens, peripheral eosinophilia and inflammatory biomarkers (sedimentation rate, C-reactive protein and lactate dehydrogenase-LDH). Patients who achieved EASI-75/EASI $\leq$ 7, SCORAD-75/SCORAD $\leq$ 24, NRS-pruritus $\leq$ 4 or DLQI $\leq$ 5 at 6 months of treatment were considered responders and those that achieved all these goals at 16 weeks were considered super-responders.

**Results:** Clinical evaluation revealed a significant reduction in median SCORAD, EASI, DLQI, NRS-pruritus and NRS-sleep over 12 months on dupilumab ( $p < 0.01$ ), in parallel with decrease in serum Th2 pathway biomarkers and LDH. All patients responded to dupilumab, and 26.7% were super-responders, supporting that dupilumab is highly effective in moderate to severe Th2-high AD.

**Conclusions:** In this cohort, none of the evaluated biomarkers at baseline were associated with a better/earlier clinical response to dupilumab. Dupilumab treatment for 52 weeks resulted in a significant and sustained reduction in blood levels of total IgE and allergen-specific IgE to aeroallergens. The potential long-term clinical benefit of these effects, even after discontinuing dupilumab therapy in patients with AD, should be explored to a greater extent.

**Keywords:** atopic dermatitis; dupilumab; IgE; LDH; Th2.

**Impact Statement:** Dupilumab proved to be effective in Th2-high AD. Sustained reduction in total IgE and aeroallergens specific IgE during 52 weeks of treatment may have long-term benefits and deserves further research.

## **Introduction**

Atopic dermatitis (AD) is the most common inflammatory skin disease. It is clinically characterized by intensely pruritic papulovesicular skin lesions that progress to scaling, depigmentation or hyperpigmentation and subsequent lichenification. AD pathophysiology is complex, involving genetic and environmental factors and it is based on a dysfunction of innate and adaptive immunity with predominantly Th2 inflammation, although it is currently recognized that Th1, Th17 and Th22 pathways also contribute to its pathogenesis (1).

Classically, AD has been classified into intrinsic and extrinsic based on total serum IgE levels and/or existence of allergic sensitization. However, this classification is too simple to comprise the different phenotypes of the disease. Different AD phenotypes have been recognized based on clinical characteristics, namely severity and chronicity of the disease, age at onset, ethnicity, race, genetic background and presence of comorbidities (2, 3). The AD endotypes can also be differentiated based on their molecular and cellular characteristics (4, 5). This heterogeneity of AD endophenotypes is associated with diverse responses to treatment.

In recent years, the main therapeutic strategies, in addition to repairing the skin barrier or influencing the microbiome, target the suppression of the Th2 inflammation pathways. A major scientific and clinical breakthrough came with dupilumab, a fully human monoclonal antibody that targets the alpha subunit of the IL-4 receptor, thereby inhibiting IL-4/IL-13 signaling, key cytokines in inflammatory Th2 diseases, like AD (6).

Clinical trials and real-life studies with dupilumab have demonstrated significant improvement in both severity scores and quality of life indexes in patients with moderate to severe AD (7). However, a subset of patients who do not respond to dupilumab has been reported; these patients may benefit from other therapeutic targets to control inflammation (1).

It is therefore necessary to characterize inflammatory and immunological endotypes of AD due to their significant implications in the stratification of disease phenotypes and for the development of targeted therapies within the scope of precision medicine, increasing the probability of achieving disease control in all patients.

In this study, we investigated the evolution of serum inflammatory biomarkers and pattern of sensitization in a group of portuguese patients with severe AD and their association with clinical response over 52 weeks of treatment with dupilumab.

## **Materials and Methods**

### Study design, population and ethical considerations

We performed a retrospective cohort study enrolling 30 patients with severe AD followed up at a Portuguese Immunoallergology Department. Criteria for initiating treatment with dupilumab included: clinical diagnosis of AD based on the Hanifin and Rajka criteria (8); moderate to severe disease with EASI (Eczema Area and Severity Index) >21 and/or SCORAD (SCORing Atopic Dermatitis) >50; uncontrolled disease despite topical therapy with corticosteroids and calcineurin inhibitors, requiring the use of systemic immunosuppressive therapy or no indication. Pregnant or breastfeeding women were excluded.

Patients over 18 years of age who completed 52 weeks with dupilumab at an initial dose of 600 mg followed by 300 mg administered every other week were included in the study. This study was conducted in accordance with ethical standards established in the Declaration of Helsinki of 1946 (9).

### Demographic, clinical and analytical data collection

Demographic and clinical data were retrieved and collected from clinical database, including age, gender, previous history of atopy as defined by the World Allergy Organization (10), onset of AD, duration of illness, atopic comorbidities and previous use of systemic therapies for AD. Objective clinical findings were assessed according to the EASI and SCORAD severity scores. The assessment of subjective symptoms was based on NRS (Numerical Rating Scale) for pruritus and sleep, and on the DLQI (Dermatological Life Quality of Life Index) quality of life scale.

Inflammatory and immunological biomarkers were analyzed, including blood eosinophil counts, sedimentation rate (SR), C-reactive protein (CRP), lactate dehydrogenase (LDH), total IgE and specific IgE (sIgE) to aeroallergens according to positive skin prick tests (wheal  $\geq$  3mm compared with the negative control) (11).

Clinical evaluation and measurement of biomarkers in peripheral blood were performed before dupilumab (T0), at 6 (T6) and 12 months of treatment (T12).

Patients who reached EASI-75 / EASI $\leq$ 7 or SCORAD-75 / SCORAD $\leq$ 24 or NRS-pruritus $\leq$ 4 or DLQI $\leq$ 5 after 6 months with dupilumab were considered responders. Patients who achieved all of these goals at 16 weeks were considered super-responders (12, 13). The association between patients' clinical and inflammatory/immunological parameters at baseline and their clinical response to dupilumab was also analyzed.

### Statistical Analysis

Statistical analysis was performed using the IBM-SPSS software package (version 25.0). Descriptive parameters such as means and standard deviations for normally distributed continuous data, frequencies, and percentages for categorical data, were calculated. Parametric quantitative data were presented as the mean and standard deviation. Non-parametric quantitative data were presented as a median

(interquartile range). Categorical data were reported as a percentage showing the proportion of positive results. Normal distribution was confirmed using Shapiro-Wilk test or skewness and kurtosis. The t-independent test or Mann Whitney test were used to compare parametric and non-parametric variables between groups (responders vs super-responders), respectively, and the paired-T or Wilcox tests to assess the evolution of biomarkers severity indexes and quality of life scores during treatment with dupilumab. Differences were considered statistically significant if  $p < 0.05$ .

## Results

### Clinical features and baseline AD severity and biomarkers

Thirty caucasian patients were included. Their mean age was  $35.7 \pm 12.4$  years (minimum 17; maximum 61) and 56.7% were female. The median duration of AD was 28 years (IQR 16.5; minimum 4; maximum 47.5).

Clinical features of the population evaluated are detailed in **table I**. All patients had other associated atopic diseases and identified allergic sensitization to aeroallergens. Most patients had undergone other systemic therapies for AD in the past, mainly cyclosporin ( $n=27$ ) and corticosteroids ( $n=29$ ) (**table I**). All patients had moderate to severe AD prior to initiation of dupilumab, with median SCORAD and EASI values of 74.2 and 29.7, respectively. Regarding self-reported scores for NRS-pruritus and NRS-sleep, their median scores and were 7. Patients reported a significant negative impact on quality of life due to AD, with a median DLQI of 19 prior to dupilumab (**table II**).

Median total serum IgE and circulating eosinophil counts at baseline was 4064 U/mL (minimum 423 U/mL, maximum 28489 U/mL) and 370/L (minimum 60/L, maximum 2020/L), respectively (**table II**). There were no differences between responders and super-responders in relation to baseline total IgE, circulating eosinophil counts, SR, CRP or LDH (**table III**).

### Clinical response to dupilumab

Overall, there was a significant reduction in EASI, SCORAD, NRS-pruritus, NRS-sleep, and DLQI over 12 months of dupilumab ( $p < 0.001$ ) (**table II**). Notably, this improvement was already significant upon 6 months treatment for all scores evaluated ( $p < 0.05$ ) (**figure 1**).

All patients reached EASI-75 /  $EASI \leq 7$ , or SCORAD-75 /  $SCORAD \leq 24$  or NRS-pruritus  $\leq 4$  or  $DLQI \leq 5$  after 6 months of dupilumab and were therefore considered responders. A subgroup of 8 patients (26.7%) achieved all these goals at 16 weeks and were classified as super-responders.

Furthermore, at baseline, 4 patients were on cyclosporine (average dose 150mg/day), and 15 patients were on systemic corticotherapy (average dose equivalent to prednisolone 12.3mg/day). After 16 weeks treatment with dupilumab, only 1 patient remained on cyclosporine and another patient on oral prednisolone for disease control. At 6 and 12 months of dupilumab, no patient was on systemic immunosuppressive therapy.

Similarly, there were no differences between responders and super-responders regarding the clinical variables analyzed at baseline, namely regarding gender prevalence, age at AD diagnosis, length of AD or the presence of atopic comorbidities. Likewise, no differences were observed between the 2 groups regarding baseline disease severity classification according to the SCORAD and EASI severity scores or inflammatory and immunological biomarkers at baseline (**table III**).

Within the group of responders at 6 months (n=22), excluding the 8 super-responders, and looking at each target criteria used to define clinical response, 12 patients (54.5%) featured an EASI-75 or  $EASI \leq 7$ , 10 (45.5%) featured a SCORAD-75 or  $SCORAD \leq 24$ , 18 (81.9%) patients reported NRS-pruritus  $\leq 4$  and 16 (72.7%) DLQI  $\leq 5$  at 6 months of treatment. Importantly, 9 patients were classified as responders only on the basis of subjective and self-reported NRS-pruritus and/or DLQI quality of life scale not meeting defined criteria for clinical response in the EASI and SCORAD disease severity indexes, and 5 of them did not reach these criteria even at 52 weeks of dupilumab, despite statistically significant reductions in the median values of these disease severity indexes throughout the treatment. This subgroup of 9 patients, that achieve symptomatic or quality of life goals but not in EASI or SCORAD response, featured significantly higher median EASI values at baseline (49.1 vs 25.8,  $p=0.027$ ). There were no other differences between this subgroup and the others responders regarding the clinical or laboratory variables analyzed at baseline.

#### Evolution of biomarkers during treatment with dupilumab

Median total serum IgE at baseline decreased significantly at 6 and 12 months of treatment ( $p<0.001$ ) (**figure 2**). Also, the median values of sIgE to mites, pollens and cat epithelium had a significant reduction over the 52 weeks of dupilumab ( $p<0.001$ ). In contrast, circulating eosinophil counts and sIgE to other aeroallergens evaluated, upon 12 months treatment did not differ significantly in relation to baseline (**table II**).

Regarding inflammation markers, there was a significant reduction in the median LDH at 12 months on dupilumab ( $p=0.002$ ), which was already observed after the first 6 months of treatment (**figure 3**). SR and CRP values did not vary significantly throughout the same period (**table II**).

The evolution of these parameters did not differ between the 2 groups, that is, there were no significant differences in the median values of the biomarkers at 6 and 12 months of dupilumab between responders and superresponders.

#### Dupilumab – associated ocular surface disease

A total of 13 patients (43.3%) developed dupilumab-associated ocular surface disease. The most frequent eye symptoms were conjunctival hyperemia (33.3%), pruritus (26.6) and dryness (16.7). Ocular surface disease developed after a mean of 19.4 weeks of dupilumab (SD 18.2; range 2-52). Most cases (84.6%) were managed with topical therapy, including corticosteroid, antihistamine, antibiotic

and cyclosporine, and 2 patients required oral doxycycline. Dupilumab dosing interval was increased to 3 or 4 weeks in 4 patients, not affecting the good response to treatment, and 1 patient permanently discontinued dupilumab at 52 weeks because of severe keratitis, after attempted interval increased to control ocular disease. A personal history of allergic conjunctivitis was found to increase the risk of developing dupilumab-associated ocular surface disease (OR 4.33 [CI 95%: 0.93-20.24],  $p=0.046$ ). Baseline SCORAD was higher in patients that developed ocular surface disease (80.7 Vs 68.5;  $p=0.046$ ). In addition, these patients featured higher median baseline eosinophils' count (595/ $\mu\text{L}$  Vs 265/ $\mu\text{L}$ ) ( $p=0.043$ ).

## Discussion

Dupilumab is available for treatment of patients with severe AD in Portugal since 2019. The present study reports the first data on the clinical outcome of dupilumab, addressing the clinical response and evolution of serum biomarkers over 52 weeks treatment with dupilumab in a group of 30 patients with moderate to severe AD under follow-up in a Portuguese immunoallergology department.

AD treatment should be guided according to severity and has been evolving towards precision/personalized medicine with the development of multiple immunological therapies, such as dupilumab. Clinical trials and real-life studies with dupilumab in AD patients have shown remarkable improvement in both severity and quality of life scores in moderate to severe AD (7).

In the present study, we also observed a significant reduction in EASI, SCORAD, NRS-pruritus, NRS-sleep, and DLQI throughout 1 year of treatment (**figure 1**), allowing in most patients clinically meaningful improvement of disease activity without the use of systemic immunosuppressive therapies.

The definition of clinical response to dupilumab has been evolving. In 2020, in a study based on data from the multicenter registry of National Expertise Center for AD from Netherlands, the relevant clinical response was measured by an improvement  $\geq 75\%$  in the EASI or a reduction in NRS-pruritus score  $\geq 4$  points or reduction in the DLQI  $\geq 4$  points compared to the baseline value (12). This means that a clinical relevant response could be defined based on thresholds in one or more outcomes of the three major AD main domains – signs, symptoms and quality of life. In that study, patients were considered to be super-responders if they showed relevant clinical improvement in these 3 domains at week 16 of treatment (12). Recently, the optimal therapeutic goals to be achieved at 6 months have been defined for each specific domain, namely, EASI-75 or EASI  $\leq 7$ , SCORAD-75 or SCORAD  $\leq 24$ , total score of the NRS-pruritus  $\leq 4$ , DLQI  $\leq 5$  and POEM (Patient Oriented Eczema Measure)  $\leq 7$  (13).

Taking this into account, the good response to dupilumab observed in our cohort is in agreement with an AD endophenotype, with predominantly Th2 inflammation, presence of allergic sensitization and with other associated atopic diseases (**table I**). In contrast, the lack of response to treatment with dupilumab would suggest other mechanisms, including impairment of the epidermal barrier, autoallergy or non-Th2 immunity underlying AD and different therapies aimed at acute-phase inflammation should

be considered (1). In fact, this cohort does not appear to illustrate the diversity of AD endotypes due to patient selection bias.

Discrepancy between the patients' subjective assessment and the physicians objective evaluation of AD control has been discussed previously (14). We thus agree with the relevance of patient perception and self-reported assessment tools when assessing response to dupilumab treatment, namely DLQI, NRS-pruritus and NRS-sleep, since it is recognized that chronic pruritus and sleep deprivation secondary to AD have a significant negative impact on the quality of life and affect different aspects such as mood, sexual activity, social interaction, work and academic activity (15,16). In our study, 9 patients were classified as responders, solely on the basis of subjective and self-reported NRS-pruritus and/or DLQI quality of life scale, while not meeting defined criteria for clinical response in the EASI and/or SCORAD disease severity scores. These patients had a significantly higher baseline EASI compared to the remaining responders, which may suggest that patients with more severe baseline disease may have a slower response to dupilumab, as improvement in pruritus usually precedes objective improvement in AD (17).

Recent studies have shown that dupilumab significantly reduced the levels of Th2 serum biomarkers in AD patients, in agreement with its mechanism of action (12, 18, 19, 20). Also in our study, we found that the median levels of total IgE, sIgE to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus Destructor*, *Phleum pratense* and cat epithelia significantly decreased at 6 and 12 months of therapy with dupilumab, probably related to its mechanism, that affects the production of IgE by blocking IgE switching cytokines (IL-4 and IL-13) on B-cells, (21). The median sIgE to *Olea europaea*, *Parietaria judaica* and dog epithelia did not differ significantly in the same period, which is likely related with the smaller number of patients sensitized to these aeroallergens in this sample (**table II**).

Of note, the median total IgE before the start of dupilumab was 4064 U/mL, and 43.3% of patients (n=13) had values above 5000 U/mL and 30% (n=9) above 10000 U/mL (**figure 1**). It is known that patients with AD often have high levels of total IgE and that more severe disease have been associated with higher levels of this biomarker (22).

We observed a significant reduction in serum LDH during treatment with dupilumab, which has already been reported in previous studies (19). As LDH is a ubiquitous intracellular enzyme, serum LDH raises by cell breakdown in almost any tissue, including the skin. Therefore, LDH can be used as a marker for tissue damage in AD, but it is extremely nonspecific (23). Although some studies have indicated that higher baseline serum LDH levels are associated with a worst response to dupilumab in AD, we did not confirm this observation in our cohort (19, 24).

Presently, there are no validated inflammatory or immunological biomarkers that can predict good or bad response to this treatment in AD patients. In the present study, there were no differences between responders and super-responders in relation to the inflammatory and immunological biomarkers analyzed at baseline, including total IgE, circulating eosinophil counts, SR, CRP and LDH.

Regarding the safety profile, dupilumab treatment is generally well tolerated, but a substantial number of patients develop ocular surface disease (over 30% in some 'real world' settings), of which most are mild-to-moderate. Topical treatment with anti-inflammatory eyedrops is often sufficient, without need to discontinue treatment (25). In our study, personal history of allergic conjunctivitis, higher baseline AD severity and higher eosinophil blood count before treatment were associated with increased dupilumab-associated ocular surface disease, as reported in clinical trials and real-life studies (26-28). Several mechanisms have been proposed for the development of this entity, namely eosinophilia after dupilumab treatment with increase in downstream activity of OX40 ligand and inhibition of IL-13 and indirect decreased production of mucin in the goblet cells of the conjunctiva. Recently, the occurrence of ocular adverse events during dupilumab therapy was also associated with a significant increase of IL-33 tear fluid levels and it has been identified a subset of memory Th2 cells that preferentially produce IL-33, related to severe itch with neuro-reconstruction in the inflammatory conjunctiva (29, 30). These mechanisms may explain the higher incidence of dupilumab-associated ocular surface disease reported in this group of patients (43.3%), all of them with a predominantly Th2 inflammation.

Despite the relatively small sample size and retrospective methodology, we highlight the relevance of our results, as the first study reporting a cohort of Portuguese patients treated with dupilumab, focusing on important aspects such as the evolution of total IgE and specific IgE to relevant allergens.

Our results reinforce previous data reporting the efficiency of dupilumab in AD, with a significant clinical improvement with reduction in EASI, SCORAD, NRS-pruritus, NRS-sleep and DLQI, in parallel with decrease in serum Th2 pathway biomarkers and LDH.

In our cohort, from a Department of Immunoallergology, 100% of patients were responders, 26.7% super-responders, supporting the high efficacy of dupilumab in moderate to severe Th2-high AD.

A subgroup of 9 patients, with a significantly higher baseline EASI compared to the remaining responders, were classified as responders only on the basis of subjective scores, suggesting that patients with more severe initial may respond more slowly to dupilumab. which will be interesting to detail over a longer period.

None of the evaluated biomarkers were associated with a better/earlier clinical response to dupilumab.

In our real-life study, dupilumab treatment for 52 weeks resulted in a significant and sustained reduction in blood levels of total serum IgE and allergen-specific IgE to mites, pollens and cat epithelium in moderate to severe AD. The potential long-term clinical benefit of these concomitant immunomodulatory effects in patients with AD, eventually maintained after increasing dose interval or discontinuing dupilumab therapy, should be deeply explored over an extended period.



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**Authors' contributions:** RL, SLS and AL designed the study and wrote the manuscript. RB and EP contributed to data collection. RL, RB, SLS and AL performed research and analysed data. All authors read and approved the final manuscript.

**Conflict of interests:** The authors declare that they have no conflict of interests.

## References

1. Werfel T, Allam JP, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016;138(2):336-49. doi: 10.1016/j.jaci.2016.06.010.
2. Wojciechowska M, Żbikowska-Gotz M, Marek-Józefowicz L, Przybyszewski M, Gocki J, Bartuzi Z. Allergic phenotypes in adult patients with atopic dermatitis, determined with the ISAC test (ImmunoCAP ISAC). *Postepy Dermatol Alergol* 2018;35(4):351-9. doi: 10.5114/ada.2018.77664.
3. Seo E, Yoon J, Jung S, Lee J, Lee BH, Yu J. Phenotypes of atopic dermatitis identified by cluster analysis in early childhood. *J Dermatol* 2019;46(2):117-23. doi: 10.1111/1346-8138.14714.
4. Noda S, Suarez-Farinas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased Th17 polarization. *J Allergy Clin Immunol* 2015;136:1254-64. doi: 10.1016/j.jaci.2015.08.015.
5. Thijs JL, Strickland I, Bruijnzeel-Koomen CAFM, Nierkens S, Giovannone B, Csomor E, et al. Moving toward endotypes in atopic dermatitis: Identification of patient clusters based on serum biomarker analysis. *J Allergy Clin Immunol* 2017;140(3):730-7. doi: 10.1016/j.jaci.2017.03.023.
6. Newsom M, Bashyam AM, Balogh EA, Feldman SR, Strowd LC. New and Emerging Systemic Treatments for Atopic Dermatitis. *Drugs* 2020;80(11):1041-52. doi: 10.1007/s40265-020-01335-7.
7. Fargnoli MC, Esposito M, Ferrucci S, Girolomoni G, Offidani A, Patrizi A, et al. Real-life experience on effectiveness and safety of dupilumab in adult patients with moderate-to- severe atopic dermatitis. *J Dermatolog Treat* 2019;28:1-7. doi: 10.1080/09546634.
8. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1980;92:44-7. doi: 10.2340/00015555924447.
9. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053.
10. Tanno LK, Calderon MA, Smith HE, Sanchez-Borges M, Sheikh A, Demoly P, on behalf of Joint Allergy Academies. Dissemination of definitions and concepts of allergic and hypersensitivity conditions. *World Allergy Organ J* 2016;9:24-32. doi: 10.1186/s40413-016-0115-2.

11. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. *Clin Transl Allergy* 2013;3(1):3. doi: 10.1186/2045-7022-3-3.
12. Ariëns LFM, van der Schaft J, Bakker DS, Balak D, Romeijn MLE, Kouwenhoven T, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry. *Allergy* 2020;75(1):116-26. doi: 10.1111/all.14080.
13. De Bruin-Weller M, Biedermann T, Bissonnette R, Deleuran M, Foley P, Girolomoni G, et al. Treat-to-Target in Atopic Dermatitis: An International Consensus on a Set of Core Decision Points for Systemic Therapies. *Acta Derm Venereol* 2021;101(2):adv00402. doi: 10.2340/00015555-3751.
14. Wei W, Anderson P, Gadkari A, Blackburn S, Moon R, Piercy J, et al. Discordance Between Physician- and Patient-Reported Disease Severity in Adults with Atopic Dermatitis: A US Cross-Sectional Survey. *Am J Clin Dermatol* 2017;18(6):825-835. doi: 10.1007/s40257-017-0284-y.
15. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol* 2017;137(1):26-30. doi: 10.1016/j.jid.2016.07.012.
16. Torres T, Gonçalo M, Paiva Lopes MJ, Claro C, Ramos L, Selores M, et al. Portuguese recommendations for the treatment of atopic dermatitis with biologic therapy and JAK inhibitors in adult patients. *Drugs Context* 2021;10:2021-9-5. doi: 10.7573/dic.2021-9-5.
17. Brás R, Limão R, Pedro E, Lopes A. Pruritus burden assessment in severe atopic dermatitis patients under dupilumab: response predictor? *Eur Ann Allergy Clin Immunol* 2023. doi: 10.23822/EurAnnACI.1764-1489.308. Epub ahead of print.
18. Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019;143(1):155-72. doi: 10.1016/j.jaci.2018.08.022.
19. Jang DH, Heo SJ, Kook HD, Lee DH, Jung HJ, Park MY, et al. A 52 weeks dupilumab treatment for moderate to severe atopic dermatitis in Korea: long-term efficacy and safety in real world. *Sci Rep* 2021;11(1):23539. doi: 10.1038/s41598-021-02950-4.
20. Hamilton JD, Harel S, Swanson BN, Brian W, Chen Z, Rice MS, et al. Dupilumab suppresses type 2 inflammatory biomarkers across multiple atopic, allergic diseases. *Clin Exp Allergy* 2021;51(7):915-931. doi: 10.1111/cea.13954.
21. Wollenberg A, Thomsen SF, Lacour JP, Jaumont X, Lazarewicz S. Targeting immunoglobulin E in atopic dermatitis: A review of the existing evidence. *World Allergy Organ J* 2021;14(3):100519. doi: 10.1016/j.waojou.2021.100519.
22. Tamagawa-Mineoka R, Katoh N. Atopic Dermatitis: Identification and Management of Complicating Factors. *Int J Mol Sci* 2020;21(8):2671. doi: 10.3390/ijms21082671.
23. Livesey A, Garty F, Shipman AR, Shipman KE. Lactate dehydrogenase in dermatology practice. *Clin Exp Dermatol* 2020;45(5):539-543. doi: 10.1111/ced.14134.

24. Kato A, Kamata M, Ito M, Uchida H, Nagata M, Fukaya S, et al. Higher baseline serum lactate dehydrogenase level is associated with poor effectiveness of dupilumab in the long term in patients with atopic dermatitis. *J Dermatol* 2020;47(9):1013-1019. doi: 10.1111/1346-8138.15464.
25. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S, et al. European guideline (EuroGuiDerm) on atopic eczema: part I - systemic therapy. *J Eur Acad Dermatol Venereol*. 2022 Sep;36(9):1409-1431. doi: 10.1111/jdv.18345.
26. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019;181(3):459-473. doi: 10.1111/bjd.17869.
27. Thyssen JP, Toft PB, Halling-Overgaard AS, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. *J Am Acad Dermatol* 2017;77(2):280-286.e1. doi: 10.1016/j.jaad.2017.03.003.
28. Nettis E, Bonzano L, Patella V, Detoraki A, Trerotoli P, Lombardo C; Italian DADReL (Dupilumab Atopic Dermatitis in Real Life) Study Group. Dupilumab-Associated Conjunctivitis in Patients With Atopic Dermatitis: A Multicenter Real-Life Experience. *J Invest Allergol Clin Immunol*. 2020;30(3):201-204. doi: 10.18176/jiaci.0481.
29. Chiricozzi A, Di Nardo L, Gori N, Antonelli F, Pinto L, Cuffaro G, et al. Dupilumab-associated ocular adverse events are predicted by low tear break-up time and correlate with high IL-33 tear concentrations in patients with atopic dermatitis. *Exp Dermatol* 2023. doi: 10.1111/exd.14859.
30. Okano M, Hirahara K, Kiuchi M, Onoue M, Iwamura C, Kokubo K, et al. Interleukin-33-activated neuropeptide CGRP-producing memory Th2 cells cooperate with somatosensory neurons to induce conjunctival itch. *Immunity* 2022;55(12):2352-2368.e7. doi: 10.1016/j.immuni.2022.09.016.

**Table I.** Demographic and clinical characterization of study population.

<b>Female, n (%)</b>		17 (56.7)
<b>Age, mean <math>\pm</math> SD [minimum-maximum], years</b>		35.7 $\pm$ 12.4 [17-61]
<b>Age at diagnosis of AD, mean <math>\pm</math> SD [minimum-maximum], years</b>		7.4 $\pm$ 10.3 [1-40]
<b>Duration of AD, median; IQR [minimum-maximum], years</b>		28; 16.5 [4-47.5]
<b>Other atopic diseases, n (%)</b>	Allergic rhinitis	30 (100)
	Allergic asthma	21 (70)
	Allergic conjunctivitis	12 (40)
	IgE mediated food allergy	7 (23)
<b>Allergic sensitization*, n (%)</b>	Mites	30 (100)
	Pollens	23 (77)
	Epithelia	14 (47)
<b>Previous use os systemic therapies for AD, n (%)</b>	Cyclosporin A	27 (90)
	Methotrexate	3 (10)
	Azathioprine	5 (17)
	Corticosteroids	29 (97)
	Omalizumab	12 (40)

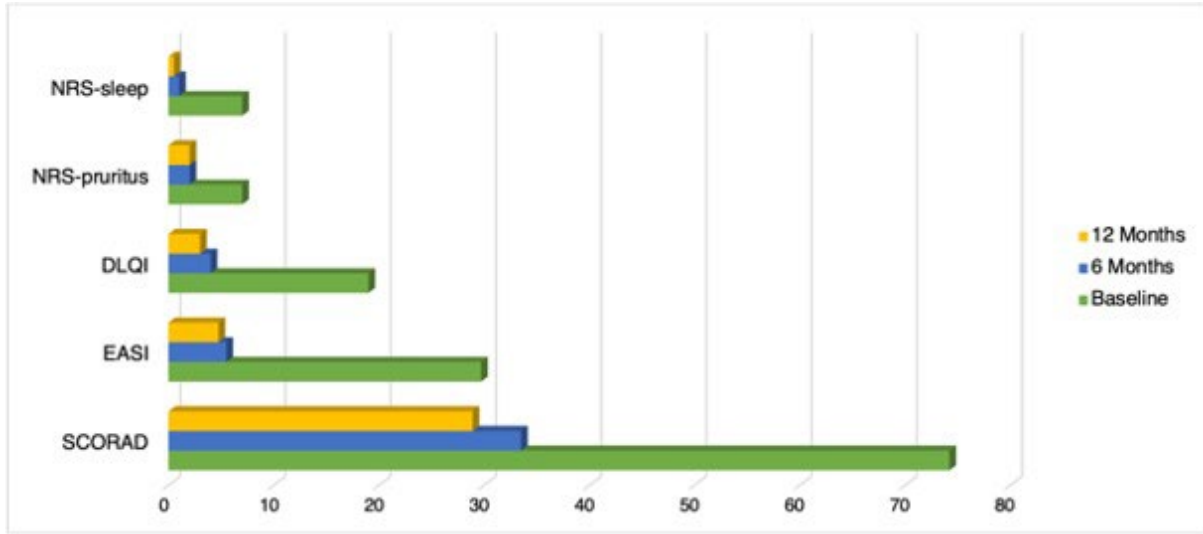
AD=Atopic dermatitis; IQR=Interquartile range; SD=Standard deviation; \*Positive skin prick test (mean wheal diameter  $\geq$ 3mm compared to negative control).

**Table II.** Evolution of AD severity indexes and biomarkers during treatment with dupilumab.

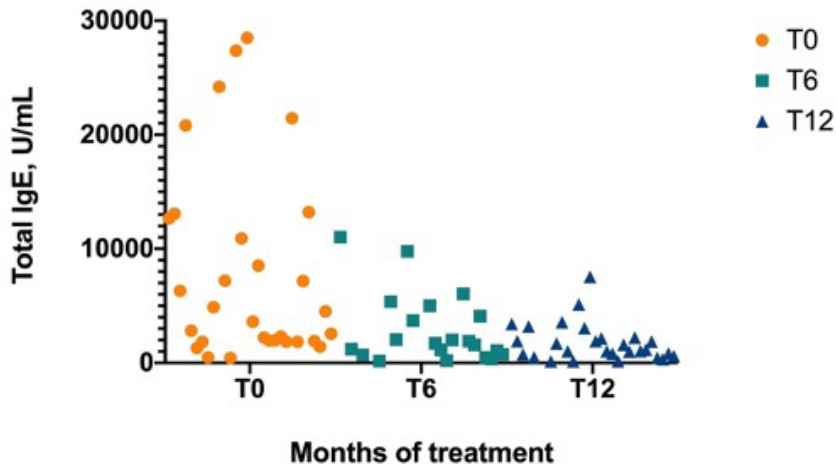
		Baseline	12 months	<i>P</i> value
<b>AD Severity indexes,</b> median [minimum- maximum]	SCORAD	74.2 [41.5-103.1]	28.9 [6.4-44.9]	<0.001
	EASI	29.7 [11.8-65.4]	4.8 [0.3-16.9]	<0.001
	DLQI	19 [4-29]	3 [0-8]	<0.001
	NRS-pruritus	7 [3-10]	2 [0-8]	<0.001
	NRS-sleep	7 [0-7]	1 [0-10]	<0.001
<b>Serum biomarkers,</b> median [minimum- maximum]	Total IgE (U/mL)	4064 [423-28489]	1892 [133-7549]	<0.001
	Eosinophil count (/L)	370 [60-2020]	465 [90-1840]	ns
	SR (mm)	12.5 [2-66]	12 [2-64]	ns
	CRP (mg/dL)	0.06 [0.03-0.38]	0.07 [0.02-3.42]	ns
	LDH (U/L)	215 [155-522]	177 [133-255]	0.002
	sIgE <i>D. pteronyssinus</i> (kU/L)	n=27 101 [9.9-101]	77.5 [1.3-101]	<0.001
	sIgE <i>D. farinae</i> (kU/L)	n=22 94.5 [11.6-101]	55.1 [1.1-101]	<0.001
	sIgE <i>Lepido. destructor</i> (kU/L)	n=24 76 [0.6-101]	19.6 [0.4-101]	<0.001
	sIgE <i>Phleum pratense</i> (kU/L)	n=19 20.3 [0.5-101]	5.73 [0.34-77.5]	<0.001
	sIgE <i>Olea europaea</i> (kU/L)	n=7 24.6 [0.37-101]	3.95 [0-86.7]	0.018
	sIgE <i>Parietaria judaica</i> (kU/L)	n=12 16.5 [0.6-70.2]	5.16 [0-55.5]	0.003
	sIgE Cat epithelia (kU/L)	n=19 39.8 [6.9-101]	17 [0.8-89.2]	<0.001
	sIgE Dog epithelia (kU/L)	n=6 45 [23.5-97]	25.1 [6.22-35.2]	ns

AD=Atopic dermatitis; CRP=C-reactive protein; DLQI= Dermatological life quality of life index; EASI=Eczema Area and Severity Index; IQR=Interquartile range; LDH=lactate dehydrogenase; NRS=Numerical Rating Scale; ns=non significant; SCORAD= SCORing Atopic Dermatitis; sIgE=specific IgE; SR=sedimentation rate.

**Figure 1.** Evolution of atopic dermatitis severity indexes during treatment with dupilumab.



**Figure 2.** Evolution of total serum IgE during treatment with dupilumab.



**Figure 3.** Evolution of LDH during treatment with dupilumab.

