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Real-life experience on effectiveness and safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis / Fargnoli, M. C.; Esposito, M.; Ferrucci, S.; Girolomoni, G.; Offidani, A.; Patrizi, A.; Peris, K.; Costanzo, A.; Malara, G.; Pellacani, G.; Romanelli, M.; Amerio, P.; Cristaudo, A.; Flori, M. L.; Motolese, A.; Betto, P.; Patruno, C.; Pigatto, P.; Sirna, R.; Stinco, G.; Zalaudek, I.; Bianchi, L.; Boccaletti, V.; Cannavo, S. P.; Cusano, F.; Lembo, S.; Mozzillo, R.; Gallo, R.; Potenza, C.; Rongioletti, F.; Tiberio, R.; Grieco, T.; Micali, G.; Persechino, S.; Pettinato, M.; Pucci, S.; Savi, E.; Stingeni, L.; Romano, A.; Argenziano, G.. - In: THE JOURNAL OF DERMATOLOGICAL TREATMENT. - ISSN 0954-6634. - 32:5(2021), pp. 507-513. [10.1080/09546634.2019.1682503]

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12/10/2024 06:13

Journal of Dermatological Treatment

ISSN: 0954-6634 (Print) 1471-1753 (Online) Journal homepage: https://www.tandfonline.com/loi/ijdt20

Real-life experience on effectiveness and safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis

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To cite this article: MC Fargnoli, M Esposito, S Ferrucci, G Girolomoni, A Offidani, A Patrizi, K Peris, A Costanzo, G Malara, G Pellacani, M Romanelli, P Amerio, A Cristaudo, ML Flori, A Motolese, P Betto, C Patruno, P Pigatto, R Sirna, G Stinco, I Zalaudek, L Bianchi, V Boccaletti, SP Cannavò, F Cusano, S Lembo, R Mozzillo, R Gallo, C Potenza, F Rongioletti, R Tiberio, T Grieco, G Micali, S Persechino, M Pettinato, S Pucci, E Savi, L Stingeni, A Romano, G Argenziano & On behalf of the Dupilumab Italian National Access Program (Dup-INAP group) (2019): Real-life experience on effectiveness and safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2019.1682503

To link to this article: https://doi.org/10.1080/09546634.2019.1682503

Accepted author version posted online: 24 Oct 2019.

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REAL-LIFE EXPERIENCE ON EFFECTIVENESS AND SAFETY OF DUPILUMAB IN ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Running head: Real-life experience with Dupilumab

Fargnoli MC,[1*] Esposito M,[1*] Ferrucci S,[2] Girolomoni G,[3] Offidani A,[4] Patrizi A,[5] Peris K,[6,7] Costanzo A,[8] Malara G,[9] Pellacani G,[10] Romanelli M,[11] Amerio P,[12] Cristaudo A,[13] Flori ML,[14] Motolese A,[15] Betto P,[16] Patruno C,[17] Pigatto P,[18] Sirna R,[19] Stinco G,[20] Zalaudek I,[21] Bianchi L,[22] Boccaletti V,[23] Cannavò SP,[24] Cusano F,[25] Lembo S,[26] Mozzillo R,[27] Gallo R,[28] Potenza C,[29] Rongioletti F,[30] Tiberio R,[31] Grieco T,[32] Micali G,[33] Persechino S,[34] Pettinato M,[35] Pucci S,[36] Savi E,[37] Stingeni L,[38] Romano A,[39] Argenziano G[40]. *On behalf of the **Dup**ilumab **I**talian **N**ational **A**ccess **P**rogram (**Dup-INAP** group).*

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KEY WORDS: atopic dermatitis, dupilumab, real-life

Word count: 2133

Number of references: 21

Number of figures: 3

Number of tables: 1

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Conflicts of interest:

P. Amerio received honoraria as a speaker and advisory board member from Sanofi-Genzyme. P. Betto has been principal investigator in clinical trials sponsored by and/or received honoraria from Sanofi-Genzyme and Sandoz. L. Bianchi has been principal investigator in clinical trials sponsored by and/or received personal fees from Sanofi Genzyme, Eli-Lilly, Abbvie. S.P. Cannavò has been principal investigator in clinical trials sponsored by and/or received personal fees from AbbVie, Celgene, Eli-Lilly, Janssen-Cilag, Leo Pharma, Novartis, Sanofi. A. Costanzo has been principal investigator in clinical trials sponsored by and/or received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Celgene, Eli-Lilly, Genzyme, Leo Pharma, Novartis, Pfizer, Regeneron, Samsung, Sandoz and Sanofi. A. Cristaudo has been principal investigator in clinical trials sponsored by Abbvie, Leo Pharma and Pfizer. F. Cusano received honoraria as speaker and advisory board member from Sanofi Genzyme. M. Esposito has served as a speaker for Sanofi-Genzyme. M.C. Fargnoli has served on advisory board, received honoraria for lectures and research grants from Sanofi-Genzyme. S. Ferrucci has been principal investigator in clinical trials sponsored by and/or received personal fees from AbbVie, Eli-Lilly, Novartis, and Sanofi. G. Girolomoni has been principal investigator in clinical trials sponsored by and/or received personal fees from AbbVie, Abiogen, Almirall, Amgen, Biogen, Celgene, Eli-Lilly, Genzyme, Leo Pharma, Menlo therapeutics, Novartis, Pfizer, Regeneron, Samsung, Sandoz and Sanofi. S. Lembo has received honoraria as a consultant and for attending an academic international meeting. G. Malara has been principal investigator in clinical trials sponsored by

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and/or received personal fees from AbbVie, Eli-Lilly, Janssen, Celgene, Sanofi and Almirall. A. Offidani has been principal investigator in clinical trials and has been paid as consultant by AbbVie, Almirall, Amgen, Celgene, Eli-Lilly, Leo Pharma, Novartis, Pfizer, Regeneroni and Sanofi. A Patrizi has served as a speaker and received honoraria from Sanofi-Genzyme for lectures, research grants and as an advisory board member. C. Patruno has been reimbursed by Sanofi for Advisory Boards and for international conference attendance. G. Pellacani has been principal investigator in clinical trials sponsored by and/or received personal fees from AbbVie, Almirall, Eli-Lilly, Leo Pharma, Novartis, and Sanofi. K. Peris has received honoraria as speaker and advisory board member from Sanofi-Genzyme. F. Rongioletti has served on advisory board, received honoraria for lectures and research grants from Novartis, AbbVie, Janssen-Cilag, Eli-Lilly, Leo Pharma, Sanofi-Genzyme. G. Stinco has been principal investigator in clinical trials, received honoraria for lectures and research grants from Novartis, AbbVie, Janssen-Cilag, Eli-Lilly, Leo Pharma, Sandoz, UCB. L. Stingeni has been principal investigator in clinical trials sponsored by and/or received personal fees from AbbVie, Almirall, Celgene, Eli-Lilly, Janssen, Novartis, and Sanofi-Genzyme. R. Tiberio has been principal investigator in clinical trials and received honoraria by Sanofi-Genzyme, Abbvie, Eli-Lilly.

Funding sources: This research was not funded.

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ABSTRACT

Background: Dupilumab, a fully human monoclonal antibody targeting the alpha subunit of IL-4 was recently approved for the treatment of moderate-to-severe atopic dermatitis (AD) in adult patients.

Objective: To assess dupilumab effectiveness and safety in adults with moderate-to-severe AD in a real-life Italian multicentre retrospective cohort.

Methods: Adult moderate-to-severe AD patients, referring to 39 Italian centres, received dupilumab in the context of a national patient access program. Disease assessment was performed at baseline, after 4 and 16 weeks of treatment using Eczema-Area-and-Severity-Index (EASI) score, itch and sleep numerical-rating-score (itch-NRS, sleep-NRS) and Dermatology-Life-Quality-Index (DLQI).

Results: A total of 109 (71M/38F) patients was studied. There was a significant reduction in EASI score, itch-NRS, sleep-NRS and DLQI from baseline to week 4 and a further significant decline to week 16. EASI 50, EASI75 and EASI90 were achieved by 59.6%, 28.4% and 9.3% of patients at 4 weeks and by 87.2 %, 60.6% and 32.4% of them at 16 weeks, respectively. Adverse events were experienced by 19.2% (21/109) of the patients and they were all mild in intensity, being conjunctivitis the most common side effect.

Conclusions: Dupilumab significantly improved disease severity, pruritus, sleep loss and quality of life with an acceptable safety profile.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 7-10% of the adult population [1]. The disease is characterized by pruritic eczematous lesions with a high heterogeneity of clinical manifestations [2]. Approximately 10% of adults with AD do not respond adequately to topical therapies and require phototherapy and/or systemic therapy [3]. Cyclosporine has been the only immunosuppressive drug approved for the treatment of AD in many countries so far, but its use is limited by potential long-term organ toxicity and ineffectiveness [4]. Second-line immunosuppressants, such as azathioprine, methotrexate and mycophenolate mofetil, represent off-label options suggested by international guidelines, but data on their long-term effectiveness and safety are lacking [5].

Th2-related cytokines, interleukin-4 (IL-4) and IL-13, play a key role in AD pathophysiology. Dupilumab is a fully human monoclonal antibody targeting the alpha subunit of IL-4 (IL-4Rα), common to IL-4 and IL-13, thus blocking signaling of both cytokines [6]. It is the first targeted biologic agent approved by FDA and EMA for the treatment of moderate-to-severe AD in adults. Randomized clinical trials demonstrated efficacy of dupilumab on objective and subjective disease parameters and on quality of life [7-9]. However, studies on real-life experience are needed to address dupilumab treatment since patients included in clinical trials represent a selected population, not reflecting clinical practice.

Aim of the present study was the retrospective assessment of dupilumab effectiveness and safety in a real-life Italian multicentre cohort of adult moderate-to-severe AD patients.

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METHODS

We retrospectively collected data of adult patients with moderate-to-severe AD treated with dupilumab from June 2018 to February 2019 at 39 dermatological referral centres in the context of a national patient access program authorized by the Italian Medical Agency. Treatment eligibility criteria were age ≥18 years, diagnosis of moderate-to-severe AD [10], Eczema-Area-and-Severity-Index [11] (EASI) ≥24, contraindication, side effects or failure in respect to cyclosporine (all established criteria for patient enrollment in the national access program by the Italian Medical Agency). No specific wash-out period was required. Patients were consecutively included in the analysis if they achieved an observation period of at least 16 weeks. Exclusion criteria were concomitant use of systemic immunomodulating agents and non-availability/incompleteness of recorded patients' data. Patients were treated with subcutaneous dupilumab at an initial loading dose of 600 mg followed by 300 mg every other week (label use). The following data were collected from medical records: demographic variables, disease pattern, AD phenotype, special locations of lesions (face, hands, genitals), comorbidities, previous treatments, changes of objective and subjective disease parameters and adverse events. Eosinophil count and total serum immunoglobulin E (IgE) levels were also collected, when available. Disease severity was assessed at baseline, after 4 and 16 weeks of treatment using EASI score (range 0-72) [11], itch and sleep numerical-rating-score (itch-NRS and sleep-NRS) (range 0-10) evaluated as peak score during the past 24 hours [12,13] and Dermatology Life Quality Index (DLQI) score (range 0-30) [14]. Patients' evaluation was performed at week 4 and 16 with a window of assessment of +/- 2 days due to timing of drug distribution.

A signed informed consent was obtained from patients allowing to extract data from clinical records. Approval of the study protocol was obtained by the Internal Review Board of the University of L'Aquila (no. 27/2019).

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Statistical analysis

All statistical analysis was conducted with last observation carried forward population to account for missing data. Descriptive statistics are given as mean, medians or proportion. Categorical variables were classified into two groups, above or below the median. Eosinophilia was defined as >500 cells/mm^3. Total IgE normal values were considered IgE < 100 kU/L. The effectiveness of treatment was evaluated at week 4 and at week 16 in terms of mean percentage change from baseline and percentage of patients with an EASI reduction ≥50%, ≥75% and ≥90% from baseline (EASI50, EASI75, EASI90).

Wilcoxon matched-pairs rank or paired T tests were used to evaluate differences between baseline and follow-ups. The relationship between IgE and EASI score was analyzed by Spearman's correlation. Fisher's exact test was used to test the association among EASI75, age, sex, body mass index (BMI), duration of disease, baseline EASI score. Statistics were performed by IBM-SPSS softwarev.25 (Chicago, USA). Differences were significant if $p < 0.05$.

RESULTS

Study population

A total of 109 (71M/38F) patients, with a mean age of 37.9 years (SD 14.7, range 19-80) was included in the study. Demographic and clinical baseline characteristics of patients are summarized in Table 1. Mean age at disease onset was 14.2 years (range 0-77, SD 17.8), mean BMI was 23.9 (range 17-34.6, SD 3.4) and the pattern of AD was persistent in 59/109 (54.1%) patients, relapsing in 27/109 (24.8%) patients and late-onset in 23/109 (21.1%). The most frequent AD phenotype was the classic adult-type with lichenified/exudative flexural

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dermatitis, often associated with head/neck eczema and/or hand/feet eczema, observed in 79/109 (72.5%) patients, followed by erythrodermic in 13/109 (13%), prurigo in 9/109 (8.2%) and nummular dermatitis in 8/109 (7.3%). Face was affected in 83/109 (76.1%) patients, hands in 67/109 (61.5%) and genitals in 25/109 (22.9%). Allergic comorbidities were mostly represented by allergic rhinitis (44.9%), asthma (38.5%), conjunctivitis (33.0%) and food allergy (15.6%). Other comorbidities including psychiatric or psychological conditions (11%), hypertension and cardiovascular disorders (9.1%) and obesity (6.4%) were less frequent. The majority of patients had been treated with cyclosporine (88.9%), followed by oral corticosteroids (88.1%), phototherapy (UVB) (45.8%), methotrexate (24.7%), azathioprine (16.5%), omalizumab (7.3%) and mycophenolate mofetil (0.9%).

Effectiveness parameters

A total of 106/109 patients completed the 16-week treatment period. Three patients discontinued treatment at week 4, due to ano-rectal bleeding for an anal ragad (1), inefficacy (1) and patient choice (1).

There was a significant reduction in EASI score, itch-NRS, sleep-NRS and DLQI score between baseline to 4 weeks and a further significant decline to 16 weeks. Mean variation of EASI (A), itch-NRS (B), sleep-NRS (C) and DLQI (D) from baseline at both week 4 and week 16 are shown in Figure 1 and EASI50, EASI75 and EASI90 results in Figure 2.

At baseline, the mean EASI score was 33.3 (SD 16.1) and was significantly reduced to 15.3 (SD 12.7) at 4 weeks and to 9.2 (SD 10.2) at 16 weeks ($p<0.001$ for all comparisons). Mean EASI score percentage reduction was 54.2% at 4 weeks and 72.5% at 16 weeks. At 4 weeks, 59.6% of patients achieved EASI50, and this percentage increased to 87.2% at 16

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weeks. EASI75 and EASI90 were achieved by 28.4% and 9.3% of patients at 4 weeks and by 60.6% and 32.4% of them at 16 weeks, respectively.

Itch-NRS had a mean value of 8.4 (SD 1.3) at baseline, 4.1 (SD 2.3) at 4 weeks and 2.5 (SD 2.6) at 16 weeks ($p<0.001$ for all comparisons). Mean itch-NRS percentage reduction was 51.5% at week 4 and 69.5% at week 16.

The mean baseline values of sleep-NRS significantly reduced from 6.9 (SD 2.5) to 3.3 (SD 2.4) at 4 weeks and to 1.9 (SD 2.2) at 16 weeks ($p<0.001$ for all comparisons). Mean sleep-NRS percentage reduction was 52.5% at 4 weeks and 72.3% at 16 weeks.

As for the quality of life index, mean DLQI score was 17.6 (SD 6.2) at baseline, 8.3 (SD 6.4) at 4 weeks and 5.4 (SD 6.2) at 16 weeks ($p<0.001$ for all comparison). Mean DLQI score percentage reduction was 52.9% at 4 weeks and 69.1% at week 16.

Sex, age, BMI, disease duration and baseline EASI were not significantly associated to EASI75 at 4 weeks ($p=0.279$; $p=0.832$; $p=0.880$, $p=0.606$, $p=0.140$, respectively) and at 16 weeks ($p=0.833$; $p=0.538$; $p=0.211$, $p=0.065$, $p=0.420$, respectively).

Eosinophilia (>500/mm^3) was detected in 36.7% (40/109) of patients at baseline, in 42.2% (46/109 patients) at week 4 and in 58.7% (64/109 patients) at week 16.

Total IgE serum levels were available in 66/109 (60.5%) patients both at baseline and at the 16-week follow-up visit. At baseline, total IgE levels were above normal in 53/66 (80.3%) patients with a mean value of 5099 x10^3 IU/L (SD 7728) that decreased in 40/53 (75%) patients to a mean value of 4059 x10^3 IU/L (SD 6708) at week 16. IgE levels were stable during treatment period in the remaining 13/53 (25%) patients.

At baseline, a positive correlation was found between total serum IgE and baseline EASI score ($r=0.33$, $p=0.002$). Moreover, significant direct correlations were observed between baseline IgE and relative reduction of EASI score at 4 weeks ($r=0.26$, $p=0.021$) and

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at 16 weeks ($p<0.001$).

Safety profile

At least one adverse event was experienced by 19.2% (21/109) of the patients and they were all mild in intensity. Conjunctivitis was the most common side effect being observed in 12/109 patients (11%), followed by arthralgia (2), headache (2), injection site reaction (2), fatigue (1), folliculitis (1) and ano-rectal bleeding for an anal ragad leading to treatment interruption (1). In our patients, conjunctivitis was mostly treated with artificial tears or hyaluronic acid eye-drops and resolved spontaneously. A pharmacologic topical approach with steroids, antimicrobials or cyclosporine, was required in a minority of the cases.

DISCUSSION

Our results confirmed the effectiveness and safety of dupilumab in a real-life setting in adult moderate-to-severe AD patients, as expressed by a significant reduction of all disease objective (EASI) (Figure 3) and subjective (itch-NRS, sleep-NRS) scores and of quality of life (DLQI) index as well as total IgE serum levels during the study period. Improvement in all effectiveness and quality of life parameters was significant between baseline and week 4 and between week 4 and week 16.

Few European real-life experiences have been reported in France, Denmark, Spain and The Netherlands [15-20]. In a small single-center observational study, dupilumab was proved to improve AD manifestations in 19 patients, in terms of global severity, pruritus, sleep loss and effect on atopic comorbidities [15]. At week 16, median SCORAD decreased by 55% and SCORAD75 was achieved by 22% of patients. A larger multicenter French study in 241 adult

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AD patients reported EASI75 in 48.8% of the patients after 3 months. A high frequency of conjunctivitis (38.2%) and eosinophilia (56.5%) with hypereosinophilia in one third of the patients and a high discontinuation rate (17.4%) characterized this patients' cohort [16]. In 43 Danish AD patients, signs and symptoms of AD improved after 3 months of dupilumab treatment with a statistically significant reduction in EASI, DLQI, pruritus and sleep VAS scores, serum IgE and LDH [17]. The overall percentage improvement of EASI was 72.4% at 1 month and 76.7% at 3 months. Main results were observed within the first month of treatment with continuous but not significant further improvement between one and three months. A Spanish real-life case series of 70 AD patients demonstrated a 79.3% EASI reduction and a decrease of pruritus VAS of 69.9% and of DLQI value of 62.8% at week 24 [18]. Long-term maintenance of response with no emerging adverse event was demonstrated in a small series of 30 Spanish patients treated with dupilumab for 52 weeks [19]. Finally, an observational study in The Netherlands described 95 patients treated with dupilumab with concomitant conventional systemic immunosuppressants in 43 patients, demonstrating that the combination regimen is an effective and safe transition to monotherapy [20].

In our real-life cohort, a 72.5% percentage reduction of the mean EASI score was achieved from baseline to week 16 with 87.2%, 60.6% and 32.4% of patients reaching EASI50, EASI75 and EASI90, respectively. The percentage of patients with EASI50 and EASI75 at week 16 was similar to that observed in clinical trials investigating dupilumab in combination with topical corticosteroids [8,9] while it was higher than in trials using dupilumab as monotherapy [7]. Concomitant treatment with topical anti-inflammatory agents is common practice in the real-life dermatological setting and our results are indeed in line with other real-life studies [17].

Dupilumab markedly improved key symptoms in AD positively influencing patient's quality of life by significantly reducing mean itch-NRS from baseline 8.4 to 2.5 at 16 weeks

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and mean sleep-NRS from baseline 6.9 to 1.9 at 16 weeks with a mean DLQI score percentage reduction of 69.1% at week 16.

In line with previous studies, the improvement in signs and symptoms was accompanied with a decrease of total serum IgE [15,17]. This finding is expected due to the specific mechanism of action of dupilumab blocking IL-4 and IL-13 known to increase IgE production. In addition, we found a positive correlation between total serum IgE and baseline EASI score and between baseline IgE and reduction of EASI score at weeks 4 and 16.

Dupilumab safety profile was favorable. Conjunctivitis, clinically confirmed by an oftalmologist, was the most frequent adverse event, observed in 11% of our patients, always mild in intensity and successfully resolved with topical therapy. History of allergic conjunctivitis was present in 9/12 cases (75%). Conjunctivitis was reported in 8.6-22.1% of AD patients in 11 dupilumab trials [21] and ranges up to 40% in real-life studies [16-19]. Management of conjunctivitis requires collaboration with experienced ophtalmologists and a graded therapeutic approach [21].

Limitations of our study include the small size of the cohort, the short follow-up period and the retrospective design of the study. On the other hand, real-world experiences of new treatments are needed since they have been only used in clinical trials in selected patients.

In conclusion, dupilumab demonstrated effectiveness in reducing disease severity, pruritus, sleep loss and improved quality of life with a favorable safety profile in our series of adult patients with moderate-to-severe, difficult-to-treat AD, confirming data of clinical trials. Further studies are needed to investigate the patterns of treatment response according to the heterogeneous AD phenotypes and the long-term effectiveness and safety of the drug.

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Table 1. Demographic and clinical baseline patients' characteristics (109 patients)

Gender	**n (%)**
Men	71 (65.1)
Women	38 (34.9)
Age	**yrs**
Mean (SD)	37.9 (14.7)
Range	19-80
Age at onset	**yrs**
Mean (SD)	14.2 (17.8)
Range	0-77
Body Mass Index	
Mean (SD)	23.9 (3.4)
Range	17-34.6
AD pattern	
Persistent	59 (54.1)
Relapsing	27 (24.8)
Late-onset	23 (21.1)
AD phenotype	
Classic adult-type	79 (72.5)
Erythrodermic AD	13 (12.0)
Prurigo	9 (8.2)
Nummular dermatitis	8 (7.3)
Allergic comorbidities	**n (%)**
Rhinitis	49 (44.9)
Asthma	42 (38.5)
Conjunctivitis	36 (33.0)
Food Allergy	17 (15.6)
Other Comorbidities	**n (%)**
Psychiatric/psychological conditions	12 (11.0)
Hypertension and other cardiovascular disorders	10 (9.1)
Obesity	7 (6.4)
Neurological disorders	6 (5.5)
Dyslipidaemia	5 (4.6)
Previous neoplastic disease	4 (3.6)
Thyroid disorders	4 (3.6)
Psoriasis	3 (2.7)
Coeliac disease	2 (1.8)
Diabetes	1 (0.9)
Previous treatments	**n (%)**
Cyclosporine	97 (88.9)
Oral Corticosteroids	96 (88.1)
Phototherapy (UVB)	50 (45.8)
Methotrexate	27 (24.7)
Azathioprine	18 (16.5)

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Omalizumab	8 (7.3)
Mycophenolate mofetil	1 (0.9)
Baseline mean EASI, value (SD)	33.3 (16.1)
Baseline mean itch-NRS, value (SD)	8.3 (1.3)
Baseline mean sleep-NRS, value (SD)	6.9 (2.5)
Baseline mean DLQI, value (SD)	17.6 (6.2)

EASI, Eczema Area and Severity Index; *NRS*, numerical rating score; *DLQI*, Dermatology Life Quality Index

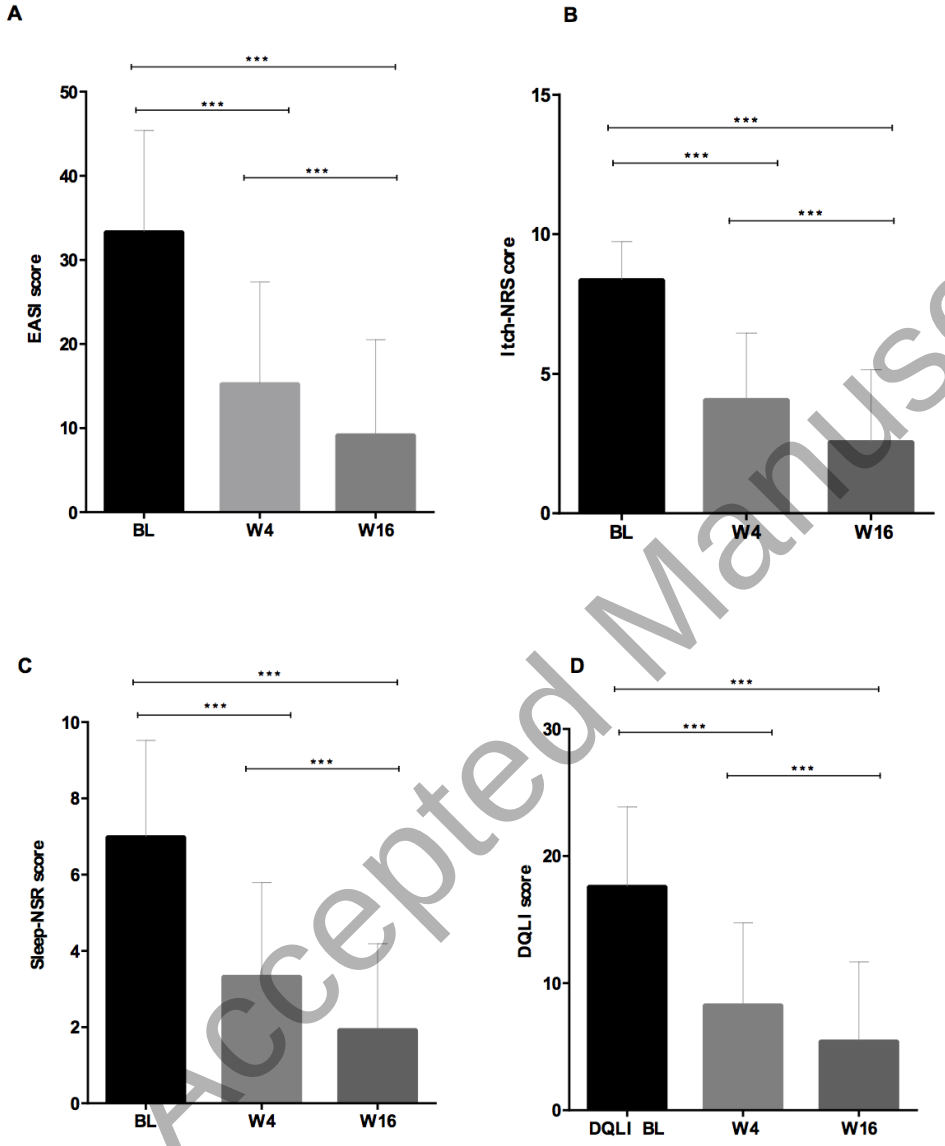

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Figure 1. Results describing improvement in terms of mean variation of EASI (A), itch-NRS (B), sleep NRS (C) and DLQI (D) at week 4 and week 16. ***p<0.0001 for all comparisons. BL, baseline; W4, week 4; W16, week 16. Thin lines refer to SD.

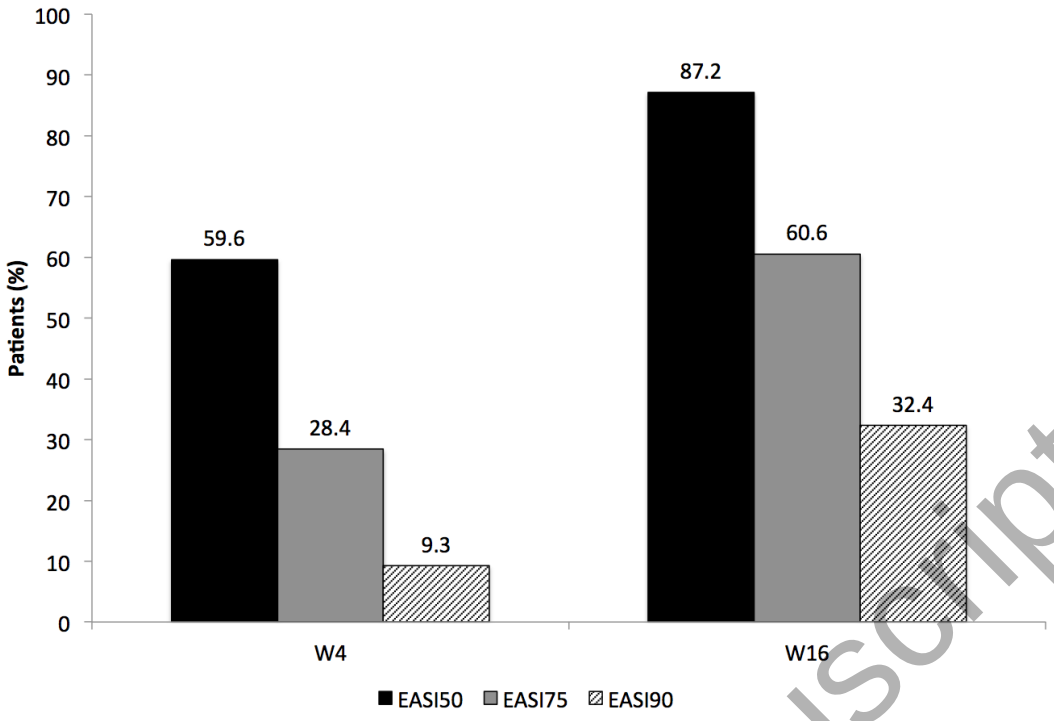

Figure 2. Percentage of patients achieving EASI50, EASI75 and EASI90 at week 4 (W4) and at week 16 (W16). Mean values are indicated on the bars.

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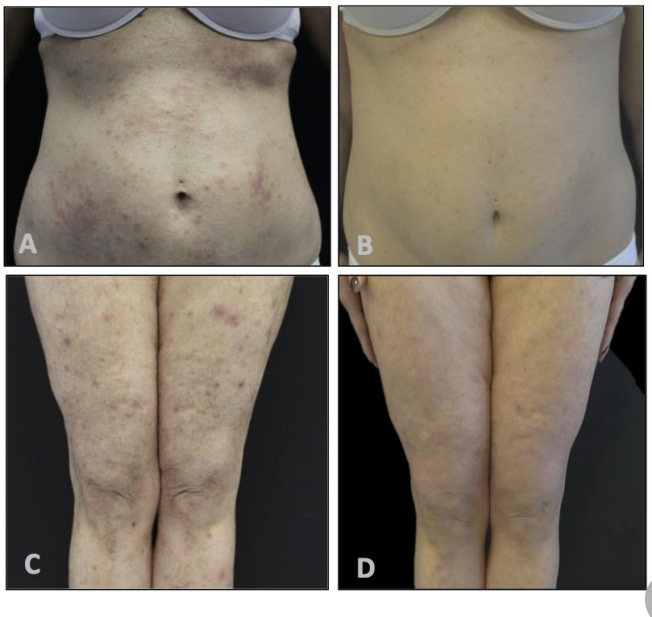

Figure 3. A 40 year-old patient affected by a persistent moderate-to-severe AD presenting with a classic adult-type phenotype before treatment (A,C - EASI score 24) and after 16 weeks of dupilumab treatment (B,D - EASI score 2).

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