



Effectiveness and Safety of Long-Term Dupilumab Treatment in Elderly Patients with Atopic Dermatitis: A Multicenter Real-Life Observational Study

Cataldo Patruno¹ · Gabriella Fabbrocini² · Giuseppe Longo³ · Giuseppe Argenziano⁴ · Silvia Mariel Ferrucci⁵ · Luca Stingeni⁶ · Ketty Peris⁷ · Michela Ortoncelli⁸ · Annamaria Offidani⁹ · Giuseppe Fabrizio Amoruso¹⁰ · Marina Talamonti¹¹ · Giampiero Girolomoni¹² · Teresa Grieco¹³ · Michela Iannone¹⁴ · Eustachio Nettis¹⁵ · Caterina Foti¹⁶ · Franco Rongioletti¹⁷ · Monica Corazza¹⁸ · Michele Delli Veneri³ · Maddalena Napolitano¹⁹ · Dupilumab for Atopic Dermatitis of the Elderly (DADE) Study Group

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Abstract

Objective The objective of this study was to assess the effectiveness and safety of dupilumab in treating elderly patients with atopic dermatitis from baseline to 52 weeks.

Methods A retrospective observational real-life study was conducted in a group of elderly patients with severe atopic dermatitis treated with dupilumab for 52 weeks. Inclusion criteria were: age ≥ 65 years; diagnosis of atopic dermatitis made by an expert dermatologist; Eczema Area and Severity Index ≥ 24 ; and a contraindication, side effects, or failure to respond to cyclosporine. The primary outcome was the mean percentage reduction in the Eczema Area and Severity Index score from baseline to week 52. Secondary measures included the mean percentage reduction in the Pruritus and Sleep Numerical Rating Scales and the Dermatology Life Quality Index, and the types and rates of adverse events from baseline to week 52.

Results One hundred and five patients were eligible for the study. Flexural dermatitis was the most frequent clinical phenotype (63.8%). The coexistence of more than one clinical phenotype was found in 70/105 (66.6%) patients. We observed a reduction in all disease severity scores from baseline to week 52 ($p < 0.001$). Adverse events were recorded in 30/105 (28.6%) patients, with conjunctivitis and injection-site reaction the most frequent.

Conclusions In this study, dupilumab is an effective and safe treatment for the long-term management of atopic dermatitis in patients aged over 65 years.

Key Points

Dupilumab is an effective and safe long-term treatment of atopic dermatitis of the adult. However, data in elderly patients (age ≥ 65 years) are limited.

In this multicenter, retrospective, observational, real-life study, 105 elderly patients with atopic dermatitis were treated with dupilumab for 52 weeks.

Dupilumab is an effective and safe treatment for the long-term management of atopic dermatitis also in elderly patients.

The members of DADE Study Group Collaborators are listed in the Acknowledgements section.

✉ Maddalena Napolitano
maddy.napolitano@gmail.com

Extended author information available on the last page of the article

1 Introduction

Recently, the long-term effectiveness and safety of dupilumab in adult patients affected by atopic dermatitis (AD) were demonstrated in clinical trials [1, 2] and in real-world studies [3–8]. However, few elderly subjects (aged ≥ 65 years) were included in these reports [2–10]. The aim of the present study was to assess the long-term effectiveness and safety of dupilumab in elderly patients with AD treated for at least 52 weeks.

2 Methods

2.1 Design and Patients

Patients' data were retrospectively collected from June 2018 to March 2020 at 17 dermatological referral Italian centers. The inclusion criteria were: age ≥ 65 years; diagnosis of AD made by an expert dermatologist; and, as required by the Italian Medicines Agency (AIFA) for dupilumab prescription, Eczema Area and Severity Index (EASI) ≥ 24 , and a contraindication, side effects, or failure to respond to cyclosporine. Patients included in the study were those who had received at least 52 weeks of dupilumab treatment, following the approved dosage schedule (600-mg induction dose, followed by 300 mg every 2 weeks). Patients who, during the study period, had used topical corticosteroids or calcineurin inhibitors as rescue treatment during dupilumab therapy were included, whereas those who had received systemic anti-inflammatory drugs (i.e., corticosteroids, cyclosporine, methotrexate, or azathioprine) or phototherapy were excluded. The following variables were monitored at baseline and at weeks 16, 32, and 52: EASI (range 0–72), Pruritus and Sleep Numerical Rating Scales [P-NRS; S-NRS] (range 0–10), and Dermatology Life Quality Index [DLQI] (range 0–30), and total serum IgE levels.

2.2 Statistics

Descriptive statistics were calculated for each demographic and clinical variable, using frequencies and percentages for categorical variables and mean $\pm$ standard deviation for continuous variables. GraphPad Prism software (Version 4.0; GraphPad Software Inc., La Jolla, CA, USA) was used for all statistical analyses. The Mann–Whitney test and Fisher test were used as appropriate to calculate statistical differences. A value of $p < 0.05$ was considered significant.

3 Results

One hundred and twelve elderly patients [69 male (61.6%); mean age 71.1 ± 6.01 years (range 65–90 years)] were treated with dupilumab. Seven (6.2%) of them were excluded

because of partial inefficacy of the drug, with a consequent addition of another systemic drug (five patients; 4.5%) or phototherapy (two patients; 1.8%). No patient dropped out because of adverse events (AEs) due to dupilumab. One hundred and five patients out of 112 (93.7%) [65 male (61.9%); mean age 70.8 ± 5.94 years (range 65–90 years)] met the inclusion criteria and were eligible for the study (Table 1). Atopic dermatitis occurred since childhood (persistent AD) in 29/105 (27.6%) patients, while in 76/105 (72.4%) patients, AD had directly started in adult age (≥ 18 years) [adult-onset AD]. The average disease duration was 19.97 ± 18.44 years (range 1–70 years). The most frequent reported atopic comorbidity was rhinitis (21/105; 20%), followed by asthma (19/105; 18.1%), conjunctivitis (12/105; 11.4%), and food allergy (5/105; 4.7%). Most patients reported these comorbidities only in past anamnesis. Other comorbidities are reported in Table 1. Flexural dermatitis was the most frequent clinical phenotype, as it was observed in 67/105 (63.8%) patients. The other clinical phenotypes were less frequent and are reported in Table 1. The coexistence of more than one clinical phenotype was found in 70/105 (66.6%) patients. Flexural dermatitis was associated with at least one other phenotype in 56/105 (53.3%) patients, the main associations being with both head/neck and hand eczema in 13/105 (12.4%) patients or solely with hand eczema in 12/105 (11.4%) patients. Regarding previous systemic treatment, systemic corticosteroids and cyclosporine were the most prescribed (Table 1).

Dupilumab treatment led to a significant reduction in the mean EASI score in the entire group of patients from baseline to weeks 16, 32, and 52 ($p < 0.0001$ for all the assessments), and from week 16 to weeks 32 and 52 ($p < 0.0001$ for both); no statistically significant differences were, instead, observed from week 32 to week 52 ($p = 0.057$) (Fig. 1). Average EASI percentage improvement from baseline was 56.0%, 83.9%, and 87.2% after 16, 32, and 52 weeks, respectively. Likewise, a significant improvement was observed in both mean P-NRS and S-NRS from baseline at all timepoints ($p < 0.0001$) and from week 16 to weeks 32 and 52, but not between weeks 32 and 52 ($p = 0.1$; $p = 0.3$). Indeed, the respective mean percentage reduction from baseline to weeks 16, 32, and 52 was 57.8%, 75.6%, and 80.3% for P-NRS, and 53.8%, 80.3%, and 82.2% for S-NRS. The DLQI score demonstrated a significant ($p < 0.0001$) decrease from baseline at all timepoints (mean percentage reduction of 54.8% at week 16, 72.0% at week 32, and 87.0% at week 52), from week 16 to weeks 32 and 52, and from week 32 to week 52 (Fig. 1).

To investigate the possible influence of patients' skin clinical features on drug effectiveness, we divided the patients into three cohorts on the basis of clinical phenotype co-occurrences: (1) flexural dermatitis phenotype (FDP) only (11/105; 10.4%); (2) clinical phenotypes other than flexural

Table 1 Baseline characteristics of elderly (aged ≥ 65 years) patients with AD ($n = 105$)

Variable	Value, n (%)
Age, years (mean $\pm$ standard deviation)	70.8 $\pm$ 5.94
Sex, male	65 (61.9)
Disease duration, years (mean $\pm$ standard deviation)	19.97 $\pm$ 18.44
AD pattern	
Persistent	29 (27.6)
Late onset (aged ≥ 18 years)	76 (72.4)
Atopic comorbidities	
Rhinitis	21 (20.0)
Asthma	19 (18.1)
Conjunctivitis	12 (11.4)
Food allergy	5 (4.7)
Other comorbidities	
Hypertension and cardiovascular disorders	62 (59.0)
Diabetes mellitus	21 (20.0)
Kidney failure	10 (9.5)
Psychiatric/psychological disorders	7 (6.6)
Benign prostatic hyperplasia	5 (2.8)
Obesity	2 (1.9)
Liver steatosis	2 (1.9)
Previous systemic treatments for AD	
Systemic corticosteroids	96 (91.4)
Cyclosporine	83 (79.1)
Phototherapy	72 (69.5)
Ustekinumab	11 (10.4)
Omalizumab	6 (5.7)
Methotrexate	4 (3.8)
Azathioprine	3 (2.9)
Mycophenolate mofetil	2 (1.9)
Apremilast	1 (1.0)
Etanercept	1 (1.0)
Clinical phenotypes ^a	
Flexural	11 (10.5)
Prurigo nodularis	8 (7.6)
Hand	7 (6.7)
Generalized	6 (5.7)
Nummular	3 (2.8)
Flexural + head/neck + hand	13 (12.4)
Flexural + hand	12 (11.4)
Flexural + head/neck	11 (10.5)
Flexural + nummular	7 (6.7)
Flexural + nummular + hand	7 (6.7)
Flexural + prurigo nodularis	6 (5.7)
Head/neck + hand	8 (7.6)
Prurigo nodularis + hand	4 (3.8)
Nummular + hand	2 (1.9)

AD atopic dermatitis

^aClinical phenotypes were defined by the main affected areas and by the characteristics of the skin lesions

dermatitis (OP) [38/105; 36.1%]; and (3) co-occurrence of the flexural phenotype with one or more than one other phenotypes (FDP + OP) [56/105; 53.3%]. In FDP patients, we observed a significant improvement of EASI from baseline to weeks 16, 32, and 52 ($p < 0.0001$ for all the assessments). However, after 16 weeks and up to 52 weeks, there was a further, but not statistically significant reduction in EASI (Fig. 2). In these patients, a similar improvement trend from baseline to weeks 16, 32, and 52 ($p < 0.0001$) was observed also for both P-NRS and S-NRS. In the OP and FDA + OP groups, a significant EASI improvement was instead recorded from baseline to all timepoints ($p < 0.0001$), and also from week 16 to weeks 32 and 52 ($p < 0.001$ and $p < 0.0001$, respectively) (Fig. 2).

We did not observe an overall significant decrease in total IgE level count ($p > 0.05$) in each group (Table 2). However, in FDP patients, we observed a constant reduction in IgE values over time, even if not statistically significant; at the same time, a substantial reduction in standard deviation was detected over time. This trend was not observed in the OP and FDP + OP groups (Table 2).

Concerning AEs, conjunctivitis was diagnosed in 14/105 patients (13.3%). On average, the first episode occurred after 12 ± 6 weeks with a resolution within week 32, mostly treated with topical corticosteroids or tacrolimus. Other AEs were flushing (5/105; 4.8%), injection-site reaction (6/105; 5.7%), fatigue (3/105; 2.9%), and alopecia (2/105; 1.9%). Twenty-five (23.8%) patients reported transient flares of dermatitis during the treatment with dupilumab, managed with topical corticosteroids and/or calcineurin inhibitors.

4 Discussion

In this study, dupilumab therapy resulted in a significant and persistent improvement in EASI, P-NRS, S-NRS, and DLQI at 52 weeks in elderly patients. In particular, an 87.2% reduction in the mean EASI score was achieved at week 52 compared with baseline. This result is similar to 73.8% reported in the long-term registration study CHRONOS [1] and 92.8% in an Italian real-life study [8]. However, it should be emphasized that the latter two studies were conducted in patients mainly under the age of 65 years and therefore not entirely comparable to our study. Furthermore, the safety profile in our study was good. Indeed, AEs were mild, conjunctivitis being the most frequent and affecting 13.3% of patients, while it was 16.4% in CHRONOS [1] and 24.1% in a real-life study [8]. No AEs required dupilumab discontinuation in any patient. The good response in terms of clinical improvement and quality of life impact appeared to be independent of the clinical phenotype, unlike what was found regarding the speed of effectiveness. Indeed, a significantly more rapid

Fig. 1 Improvement in terms of mean variation of the Eczema Area and Severity Index (EASI), Pruritus Numerical Rating Score (P-NRS), Sleep Numerical Rating Score (S-NRS), and Dermatology Life Quality Index (DLQI) from baseline to weeks 16, 32, and 52 in 105 elderly (aged ≥ 65 years) patients treated with dupilumab. Mean values of EASI, S-NRS, P-NRS, and DLQI of the study population before (week 0) and after 16 weeks (week 16) of dupilumab treatment. Statistical significance was assessed by the Mann–Whitney test and Fisher test, *** $p < 0.0001$. *ns* not significant

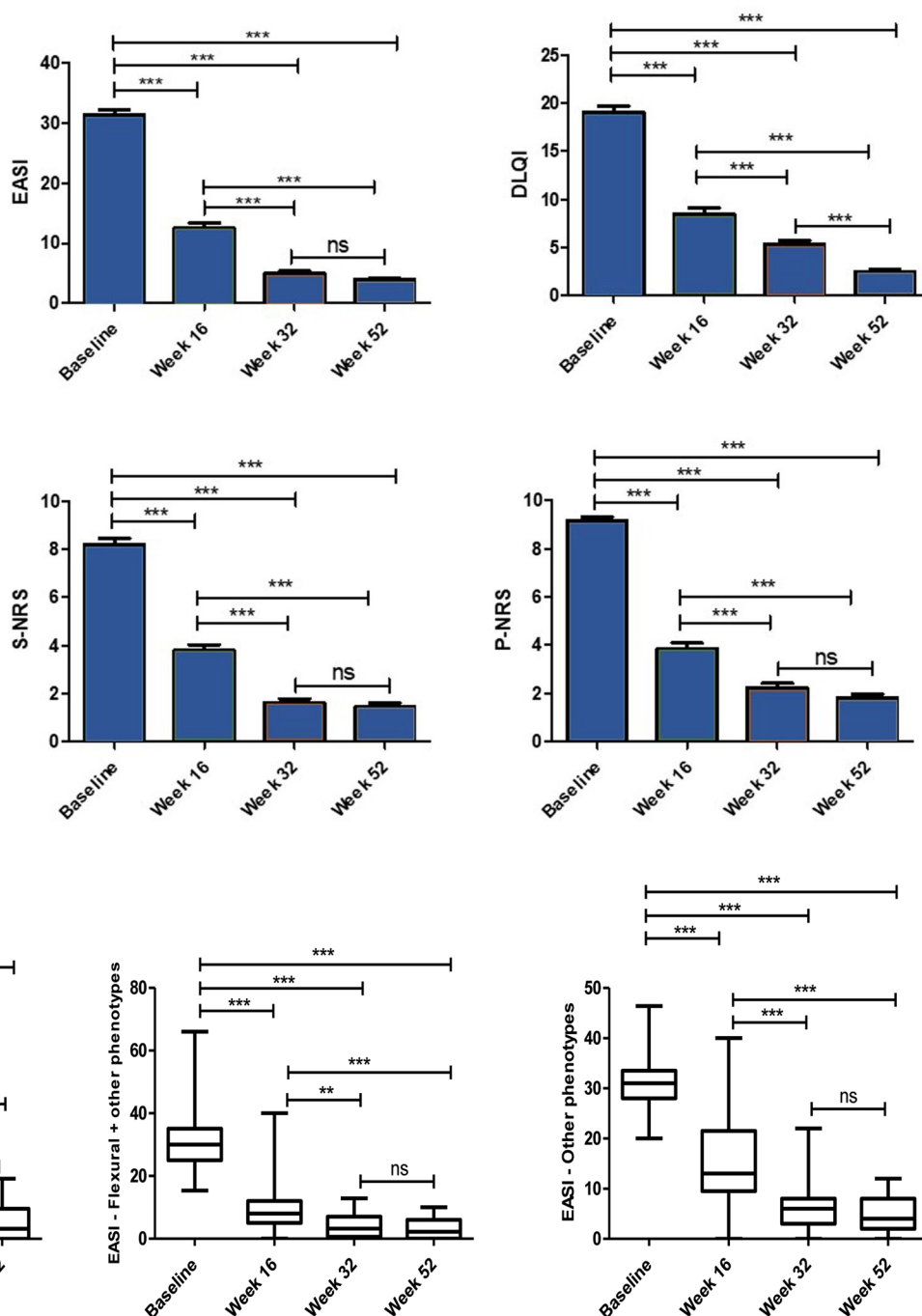


Fig. 2 Mean variation of the Eczema Area and Severity Index (EASI) from baseline to weeks 16, 32, and 52 in 105 elderly (aged ≥ 65 years) patients treated with dupilumab. They were arranged into three groups according to the clinical phenotype: (1) flexural dermatitis ($n = 11$); (2) flexural dermatitis associated with one or more than one

other phenotype ($n = 56$); and (3) phenotype other than flexural dermatitis ($n = 38$). Mean values of EASI of the three clinical phenotypes group before and after 16, 32, and 52 weeks of dupilumab treatment. Statistical significance was assessed by the Mann–Whitney test and Fisher test, *** $p < 0.0001$. *ns* not significant

response was observed at 16 weeks in the group of FDP patients compared with the OP and FDA + OP groups. However, a stable trend of improvement was recorded from

weeks 16 to 52, without statistically significant changes over time and among the phenotype groups. Furthermore,

Table 2 Trend of IgE (KU/L) from baseline to weeks 16, 32, and 52 in 105 elderly (aged ≥ 65 years) patients with AD treated with dupilumab. The patients are grouped according to the clinical phenotype: flexural dermatitis alone ($n = 56$); flexural dermatitis associated with another phenotype ($n = 11$); patients with a phenotype different from flexural dermatitis ($n = 38$)

	Total IgE (KU/L), mean $\pm$ SD			
	Baseline	Week 16	Week 32	Week 52
Flexural dermatitis	790 $\pm$ 900	525 $\pm$ 722	398 $\pm$ 476	203 $\pm$ 158
Flexural dermatitis + another phenotype	611 $\pm$ 609	505 $\pm$ 505	455 $\pm$ 472	433 $\pm$ 412
Other phenotype	654 $\pm$ 695	455 $\pm$ 428	481 $\pm$ 343	467 $\pm$ 341

SD standard deviation

dupilumab could have a stabilizing effect on IgE especially in elderly patients with FDP type AD.

5 Conclusions

Atopic dermatitis can also affect the elderly. The clinical pictures can be variable and often severe, causing a significant impairment of the quality of life. Therefore, in these cases, long-term systemic treatment is required. This is not always easy because traditional anti-inflammatory drugs can have AEs, especially in elderly patients who often have comorbidities. Although this study has some limitations, including the retrospective nature and the low number of patients, it seems to suggest that dupilumab is an effective and safe drug in these patients, even when used long term.

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Declarations

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Conflict of interest Cataldo Patruno acted as investigator, speaker, consultant, and advisory board member for AbbVie, Eli Lilly, Novartis, Pfizer, Pierre Fabre, and Sanofi. Gabriella Fabbrocini has been the principal investigator in clinical trials sponsored by and/or has received personal fees from AbbVie, Abiogen, Almirall, Celgene, Eli-Lilly, Leo Pharma, Novartis, Sanofi, and UCB. Silvia Mariel Ferrucci is a speaker for Novartis and Sanofi Genzyme, is a principal investigator for Eli Lilly, AbbVie, and Sanofi Genzyme, and is an advisory member of Sanofi Genzyme. Luca Stingeni acted as a speaker and board member for Sanofi-Genzyme. Ketty Peris reports grants and personal fees from Almirall and AbbVie, and personal fees from Biogen, Lilly, Celgene, Galderma, Leo Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz, Sun Pharma, and Janssen, outside the

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Ethics approval The Ethics Committee of University of Naples Federico II (Naples, Italy) approved this study (Approval no. CE 116/20).

Consent to participate Informed consent was obtained from all individual participants involved in the study.

Consent for publication Consent for publication was obtained from both all individual participants and authors involved in the study.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions CP, GF, and MN designed the study; GA, SF, LS, KP, MO, AO, GFA, MT, TG, MI, FR, and MC contributed to implementation of the research; GL and MDV contributed to the analysis of the results; and CP and MN wrote the manuscript in consultation with GF, GG, and EN.

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Authors and Affiliations

Cataldo Patruno¹ · Gabriella Fabbrocini² · Giuseppe Longo³ · Giuseppe Argenziano⁴ · Silvia Mariel Ferrucci⁵ · Luca Stingeni⁶ · Ketty Peris⁷ · Michela Ortoncelli⁸ · Annamaria Offidani⁹ · Giuseppe Fabrizio Amoroso¹⁰ · Marina Talamonti¹¹ · Giampiero Girolomoni¹² · Teresa Grieco¹³ · Michela Iannone¹⁴ · Eustachio Nettis¹⁵ · Caterina Foti¹⁶ · Franco Rongioletti¹⁷ · Monica Corazza¹⁸ · Michele Delli Veneri³ · Maddalena Napolitano¹⁹  · Dupilumab for Atopic Dermatitis of the Elderly (DADE) Study Group

¹ Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy

² Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

³ Department of Physics, University of Naples Federico II, Naples, Italy

⁴ Dermatology Unit, University of Campania, Naples, Italy

⁵ Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

⁶ Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy

⁷ Dermatology, University of the Sacred Heart, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy

⁸ Dermatology Clinic, University of Turin, Turin, Italy

⁹ Dermatology Unit, Department of Clinical and Molecular Sciences, Polytechnic Marche University, Ancona, Italy

¹⁰ UOC Dermatologia, AO Cosenza, Cosenza, Italy

¹¹ Dermatology Unit, Policlinico Tor Vergata, Department of Systemic Medicine, Tor Vergata University of Rome, Rome, Italy

¹² Section of Dermatology, Department of Medicine, University of Verona, Verona, Italy

¹³ Dermatology Unit, Sapienza University of Rome, Rome, Italy

¹⁴ Department of Dermatology, University of Pisa, Pisa, Italy

¹⁵ Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari Aldo Moro, Bari, Italy

¹⁶ Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy

¹⁷ Unit of Dermatology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

¹⁸ Section of Dermatology and Infectious Diseases, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

¹⁹ Department of Medicine and Health Sciences Vincenzo Tiberio, University of Molise, Via Francesco De Santis, snc., 86100 Campobasso, Italy