



## ORIGINAL ARTICLE

# Dupilumab therapy of atopic dermatitis of the elderly: a multicentre, real-life study

C. Patruno,<sup>1</sup> M. Napolitano,<sup>2,\*</sup> G. Argenziano,<sup>3</sup> K. Peris,<sup>4,5</sup> M. Ortoncelli,<sup>6</sup> G. Girolomoni,<sup>7</sup> A. Offidani,<sup>8</sup> S.M. Ferrucci,<sup>9</sup> G.F. Amoroso,<sup>10</sup> M. Rossi,<sup>11</sup> L. Stingeni,<sup>12</sup> G. Malara,<sup>13</sup> T. Grieco,<sup>14</sup> C. Foti,<sup>15</sup> M. Gattoni,<sup>16</sup> C. Loi,<sup>17</sup> M. Iannone,<sup>18</sup> M. Talamonti,<sup>19</sup> G. Stinco,<sup>20</sup> F. Rongioletti,<sup>21</sup> P.D. Pigatto,<sup>22</sup> A. Cristaudo,<sup>23</sup> E. Nettis,<sup>24</sup> M. Corazza,<sup>25</sup> F. Guarneri,<sup>26</sup> P. Amerio,<sup>27</sup> M. Esposito,<sup>28</sup> A. Belloni Fortina,<sup>29</sup> C. Potenza,<sup>30</sup> G. Fabbrocini,<sup>31</sup> DADE - Dupilumab for Atopic Dermatitis of the Elderly study group<sup>†</sup>

<sup>1</sup>Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy

<sup>2</sup>Department of Medicine and Health Sciences Vincenzo Tiberio, University of Molise, Campobasso, Italy

<sup>3</sup>Dermatology Unit, University of Campania, Naples, Italy

<sup>4</sup>Dermatology, University of the Sacred Heart, Rome, Italy

<sup>5</sup>Fondazione Policlinico Universitario A.Gemelli, IRCCS, Rome, Italy

<sup>6</sup>Dermatology Clinic, University of Turin, Turin, Italy

<sup>7</sup>Section of Dermatology, Department of Medicine, University of Verona, Verona, Italy

<sup>8</sup>Dermatology Unit, Department of Clinical and Molecular Sciences, Polytechnic Marche University, Ancona, Italy

<sup>9</sup>Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

<sup>10</sup>AO Cosenza, UOC Dermatologia, Cosenza, Italy

<sup>11</sup>UO Dermatologia, ASST Spedali Civili di Brescia, Brescia, Italy

<sup>12</sup>Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy

<sup>13</sup>Struttura Complessa di Dermatologia, Grande Ospedale Metropolitano 'Bianchi Melacrino Morelli', Reggio Calabria, Italy

<sup>14</sup>Dermatology Unit, Sapienza University of Rome, Rome, Italy

<sup>15</sup>Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy

<sup>16</sup>Dermatologic Department, S. Andrea Hospital Vercelli, Vercelli, Italy

<sup>17</sup>Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

<sup>18</sup>Department of Dermatology, University of Pisa, Pisa, Italy

<sup>19</sup>Dermatology Unit, Policlinico Tor Vergata, Department of Systemic Medicine, Tor Vergata University of Rome, Rome, Italy

<sup>20</sup>Department of Medicine, Institute of Dermatology, University of Udine, Udine, Italy

<sup>21</sup>Unit of Dermatology, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

<sup>22</sup>Department of Medical, Surgical and Odontoiatric Science, IRCCS Ospedale Ortopedico Galeazzi, Milano, Italy

<sup>23</sup>San Gallicano Dermatologic Institute IRCCS, Rome, Italy

<sup>24</sup>Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari - Aldo Moro, Bari, Italy

<sup>25</sup>Section of Dermatology and Infectious Diseases, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

<sup>26</sup>Department of Clinical and Experimental Medicine, Dermatology, University of Messina, Messina, Italy

<sup>27</sup>Dermatologic Clinic, SS. Annunziata Hospital, Chieti, Italy

<sup>28</sup>Dermatology, Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

<sup>29</sup>Unit of Dermatology, Department of Medicine DIMED, University of Padua, Padua, Italy

<sup>30</sup>Dermatology Unit 'Daniele Innocenzi', Department of MEDICO-Surgical Sciences and Bio-Technologies, Sapienza University of Rome, Fiorini Hospital, Polo Pontino, Terracina, Italy

<sup>31</sup>Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Napoli, Italy

\*Correspondence: M. Napolitano. E-mail: maddy.napolitano@gmail.com

## Abstract

**Background** Treatment of moderate-to-severe atopic dermatitis (AD) in the elderly may be challenging, due to side-effects of traditional anti-inflammatory drugs and to comorbidities often found in this age group. Furthermore, efficacy and safety of innovative drugs such as dupilumab are not yet well known.

**Objectives** A multicentre retrospective, observational, real-life study on the efficacy and safety of dupilumab was conducted in a group of patients aged  $\geq 65$  years and affected by severe AD. Their main clinical features were also examined.

<sup>†</sup>see Appendix 1

**Methods** Data of elderly patients with severe (EASI  $\geq 24$ ) AD treated with dupilumab at label dosage for 16 weeks were retrospectively collected. Treatment outcome was assessed by comparing objective (EASI) and subjective (P-NRS, S-NRS and DLQI) scores at baseline and after 16 weeks of treatment.

**Results** Two hundred and seventy-six patients were enrolled in the study. They represented 11.37% of all patients with severe AD. Flexural eczema was the most frequent clinical phenotype, followed by prurigo nodularis. The coexistence of more than one phenotype was found in 63/276 (22.82%) subjects. Data on the 16-week treatment with dupilumab were available for 253 (91.67%) patients. Efficacy of dupilumab was demonstrated by a significant reduction of all the scores. No statistically significant difference regarding efficacy was found in elderly patients when compared to the group of our AD patients aged 18–64 years, treated with dupilumab over the same period. Furthermore, only 18 (6.52%) patients discontinued the drug due to inefficacy. Sixty-one (22.51%) patients reported adverse events, conjunctivitis and flushing being the most frequent. One (0.36%) patient only discontinued dupilumab due to an adverse event.

**Conclusions** Therapy with dupilumab led to a significant improvement of AD over a 16-week treatment period, with a good safety profile. Therefore, dupilumab could be considered as an efficacious and safe treatment for AD also in the elderly.

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### Conflict of interest

C.P. acted as speaker, consultant and advisory board member for AbbVie, Novartis, Pfizer and Sanofi. M.N. acted as speaker, consultant and advisory board member for Sanofi, Abbvie, Leo Pharma and Novartis. K.P. 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 submitted work. M.O acted as speaker for AbbVie, Novartis, Sanofi. G.G. has been principal investigator in clinical trials sponsored by and/or and has received personal fees from AbbVie, Abiogen, Almirall, Alphasights, Amgen, Biogen, Bristol-Meyers Squibb, Celgene, Celltrion, Eli Lilly, Genzyme Gerson Lehrman Group, Guidepoint Global, Leo Pharma, Menlo Therapeutics, Novartis, OM Pharma, Pfizer, Regeneron, Samsung, Sandoz and UCB. A.O. acted as advisory board member, investigator, speaker for AbbVie, Celgene, Eli Lilly, Galderma, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme. S.M.F. is speaker of Novartis and Sanofi Genzyme, is principal investigator for Eli Lilly, AbbVie, Sanofi Genzyme and is an advisory member of Sanofi Genzyme. L.S acted as speaker and board member for Sanofi Genzyme. C.F acted as speaker for AbbVie, Novartis, Sanofi. G.S. has been principal investigator in clinical trials sponsored and received honoraria for lectures and research grants from Novartis, AbbVie, Janssen-Cilag, Eli Lilly, Leo Pharma, Sandoz, UCB. F.R. acted as board advisor member for Sanofi. E.N. in the past 5 years accepted a fee for organizing education for Sanofi. F.G acted as advisory board member for Sanofi. P.A. acted as speaker for Sanofi. M.E. acted as a consultant, speaker and/or board member for Eli Lilly, Novartis, Janssen, Sanofi Genzyme, UCB. C.P. acted as consultant and speaker for AbbVie, Almirall, Celgene, Leo Pharma, Novartis, Pfizer, Parexel, Sanofi, Janssen, Lilly. G.F. has been principal investigator in clinical trials sponsored by and/or and has received personal fees from AbbVie, Abiogen, Almirall, Celgene, Eli Lilly, Leo Pharma, Novartis, Sanofi, and UCB.

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### Introduction

Atopic dermatitis (AD) is a chronic disease in which the genetic impairment of skin barrier function and abnormal immune response leads to a complex reaction to environmental factors.<sup>1</sup> The worldwide prevalence of AD increased two to threefold over the past 30 years,<sup>2</sup> with high prevalence in both children (15–30%) and adults (2–10%).<sup>1,2</sup> Few studies have described so far the clinical presentation and prevalence of AD in elderly patients ( $\geq 65$  years).<sup>3,4</sup> Ageing could theoretically be associated with a higher prevalence of AD. Indeed, ageing is associated with

reduced physical skin barrier function, including decreased barrier repair and downregulation of structural proteins such as filaggrin, claudin-1 and occludin, which overall could contribute to AD in older patients.<sup>5</sup> Moreover, innate and adaptive immunity changes of ageing (so-called inflammaging) show some overlap with hallmarks observed in AD.<sup>1</sup>

Recently, elderly AD has been considered as a distinguishing clinical type of AD. In this age group, flexural dermatitis is characterized by the so-called reverse sign of lichenified eczema at the antecubital and popliteal fossae, while in younger adults,

eczema is localized in the creases of the folds.<sup>6,7</sup> Furthermore, AD can present in the elderly with atypical clinical phenotypes such as prurigo nodularis, nummular eczema or generalized eczema, more frequently than in other age groups.<sup>8</sup> On the other hand, older patients often suffer from asteatosis and pruritus due to physiologic skin ageing and comorbidities for which they take medications that might worsen pruritus and dry skin.<sup>1,7</sup> Diagnosis of AD may be difficult in these subjects for all these reasons. Consequently, diagnosis for elderly patients may be delayed up to 6 months. In fact, symptom assessment and exclusion of other conditions, including cutaneous T-cell lymphoma, allergic contact dermatitis, scabies or adverse drug reactions, are needed in this condition.<sup>1,6,7</sup>

Treatment of elderly AD can be very challenging. This is due to age-related factors such as comorbidities, use of several medications or increased risk of infection, often complicating treatment.<sup>9,10</sup> Indeed, systemic immunosuppressive therapies for the treatment of adult AD, namely cyclosporine A (CsA), methotrexate (MTX) or azathioprine, are often contraindicated or counterproductive in the elderly.<sup>9</sup> Noteworthy, CsA is the only systemic immunosuppressive drug labelled for AD in Italy. Dupilumab is a monoclonal antibody to the shared alpha subunit of the interleukin (IL)-4 and IL-13 receptor. It is approved in Europe for the treatment of moderate-to-severe AD in adult patients, after CsA treatments have failed or in case of CsA contraindications.<sup>11</sup> In one randomized controlled trial, dupilumab exhibited a similar favourable safety profile and efficacy in all age groups of patients, including the elderly.<sup>12</sup> One case-series study in real life confirmed this aspect.<sup>4</sup> The aim of this multicentre retrospective, observational, real-life study was to evaluate the clinical features of AD patients aged  $\geq 65$  years and the potential benefit and safety of dupilumab in an Italian population.

## Methods

Data of elderly (age  $\geq 65$  years) patients with AD treated with dupilumab were retrospectively collected from June 2018 to March 2020 at 27 dermatological referral centres homogeneously distributed in Northern, Central and Southern Italy. Inclusion criteria were as follows: age  $\geq 65$  years, diagnosis of AD made by an expert, board-certified dermatologist; Eczema Area and Severity Index (EASI)  $\geq 24$ ; contraindication, side-effects or failure to CsA. These treatment criteria are established for patient enrolment in the dupilumab drug prescription appropriateness according to the Italian Medical Agency. A washout period was not required. Dupilumab was administered subcutaneously at label dosage (600 mg induction dose, followed by 300 mg every 2 weeks). Patients with an observational period of at least 16 weeks were consecutively included in the study.

The following demographic and clinical data were recorded: age, sex, medical history, clinical phenotype of AD, comorbidities (atopic and non-atopic), concomitant medications or procedures, adverse events (AEs) and efficacy outcomes to previous treatments. Disease severity was assessed at baseline and after

16 weeks of dupilumab therapy using EASI (range 0–72), pruritus and sleep numerical rating score [P-NRS and S-NRS (range 0–10)] evaluated as peak score during the past 7 days and Dermatology Life Quality Index (DLQI) score (range 0–30). Eosinophil count and total serum immunoglobulin E (IgE; normal range:  $0\text{--}150 \times 10^3$  IU/L) levels were collected.

The Ethics Committee of the coordinating centre (University of Naples Federico II) approved the study protocol. A signed informed consent was obtained from each patient. Unpaired Student's *t*-test was used to calculate statistical differences.  $P < 0.05$  was considered statistically significant. GraphPad Prism software (v.4.0; GraphPad Software Inc. La Jolla, CA, USA) was used for all statistical analyses.

## Results

A total of 2428 AD adult patients [1363 males (56.14%); mean age  $41.05 \pm 19.70$  years (range 18–91)] had been treated with dupilumab during the reference period. Of these, 2152 patients (1204 males; mean age  $39.64 \pm 10.23$ ) were aged 18–64 years and 276 patients (11.37%; 159 males)  $>65$  years (mean age  $73.06 \pm 6.83$  years; range 65–91 years). The latter 276 elderly patients were enrolled in the study. The demographic and clinical baseline characteristics of the group of elderly patients are reported in Table 1. Clinical manifestations of AD occurred before the age of 18 (persistent AD) in 71/276 (25.72%) patients, while in 205/276 (74.28%) after that age (late-onset AD;  $P < 0.01$ ), with an average duration of the disease of  $18.4 \pm 19.8$  years (range 1–77).

Flexural dermatitis was the most frequent AD phenotype and was observed in 125/276 (45.28%) patients, followed by prurigo nodularis (67/276; 24.28%), head/neck eczema 58/276 (21.01%), generalized eczema (43/276; 15.58%), hand eczema 30/276 (10.87%), nummular eczema (20/276; 7.25%) and erythroderma (11/276; 3.99%). The coexistence of more than 1 phenotype was found in 63/276 (22.82%) patients. The main associations were flexural dermatitis with head/neck eczema or hand eczema in 21 (7.61%) and 18 (6.52%) patients, respectively, and with both head/neck and hand eczema in 12 (4.35%) patients. No statistically significant differences were found regarding AD phenotype between persistent and adult-onset AD group, except for prurigo nodularis ( $P < 0.01$ ). Indeed, 58 (86.57%) of 67 patients with prurigo nodularis phenotype belonged to the adult-onset group with an average age at onset of  $47.4 \pm 11.6$  years.

The most frequent reported atopic comorbidity was rhinitis (47/276; 17.03%), followed by asthma (35/276; 12.68%), conjunctivitis (35/276; 12.68%) and food allergy (10/276; 3.62%). Other main comorbidities were hypertension and cardiovascular disorders (121/276; 43.84%), diabetes (43/276; 15.58%) and chronic kidney failure (20/276; 7.25%). Psychiatric or psychological conditions, such as depression or mixed anxiety–depressive disorder (16/276; 5.80%), were less frequent. Twenty-seven out of 276 (9.78%) patients reported a personal history of cancer.

**Table 1** Demographic and clinical baseline characteristics of AD elderly ( $\geq 65$  years) patients treated with dupilumab ( $n = 276$ )

Variable	Value n (%)
Age (year)	73.06 $\pm$ 6.83
Sex, male	159 (57.61)
Duration of AD (year)	18.4 $\pm$ 19.8
<b>AD pattern</b>	
Persistent	71 (25.72)
Late onset ( $\geq 18$ years)	205 (74.28)
<b>AD phenotype</b>	
Lichenified/exudative flexural dermatitis	125 (45.28)
Prurigo nodularis	67 (24.28)
Head/neck eczema	58 (21.01)
Generalized eczema	43 (15.58)
Hand eczema	30 (10.87)
Nummular dermatitis	20 (7.25)
Erythroderma	11 (3.99)
<b>Clinical scores</b>	
EASI score	29.2 $\pm$ 8.7
Peak score on NRS for pruritus	8.9 $\pm$ 1.6
Peak score on NRS for sleep	7.8 $\pm$ 1.8
DLQI score	18.4 $\pm$ 4.7
<b>Atopic comorbidities</b>	
Rhinitis	47 (17.03)
Asthma	35 (12.68)
Conjunctivitis	35 (12.68)
Food allergy	10 (3.62)
<b>Other comorbidities</b>	
Hypertension and cardiovascular disorders	121 (43.84)
Diabetes	43 (15.58)
Chronic kidney failure	20 (7.25)
Psychiatric/psychological disorders	16 (5.80)
Thyroid disease	15 (5.43)
Benign prostatic hyperplasia	10 (3.62)
Obesity	10 (3.62)
Psoriasis	7 (2.54)
Liver steatosis	5 (1.81)
<b>Previous systemic treatments for AD</b>	
Cyclosporine	158 (57.25)
Systemic corticosteroids	115 (41.67)
Phototherapy	108 (39.13)
Methotrexate	18 (6.52)
Omalizumab	10 (3.62)
Apremilast	9 (3.26)
Ustekinumab	7 (2.54)
Other systemic treatments	8 (2.90)

AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, numerical rating score.

Before enrolment, all the patients had received at least one systemic treatment for AD. Namely, 158/276 (57.25%) had been treated with CsA, 115/276 (41.67%) with systemic

corticosteroids and 108/276 (39.13%) with phototherapy (narrow-band UVB). AD off-label treatment had been prescribed in 52/276 (18.84%) subjects: MTX in 18 (6.52%), omalizumab in 10 (3.62%), apremilast in 9 (3.26%), ustekinumab in 7 (2.54%) and other drugs in 8 (2.9%); all these drugs had been prescribed before the availability of dupilumab in Italy.

### Discontinuation of dupilumab

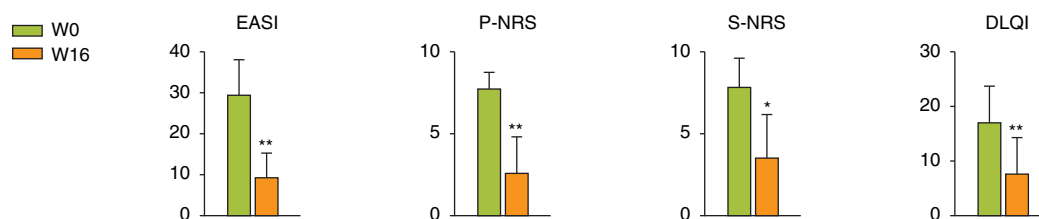
In our cohort, 23/276 (8.33%) patients discontinued dupilumab before the target treatment period (week 16). Eighteen (6.52%) out of these patients discontinued therapy because of inefficacy after an average of 12-week treatment. The other reasons of dropout were patient choice (3; 1.09%), generalized lymphadenomegaly (1; 0.36%) and death not related to the treatment or to the disease (1; 0.36%).

### Effectiveness parameters

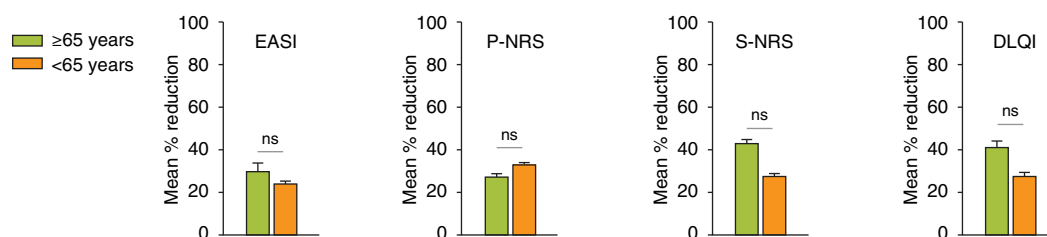
A total of 253/276 (91.67%) patients completed the observation period (16 weeks). A significant improvement in EASI score, P-NRS, S-NRS and DLQI was observed after 16 weeks of treatment with dupilumab (Fig. 1). The mean EASI score at baseline was 29.2  $\pm$  8.7 and significantly reduced to 9.1  $\pm$  6.3 at 16 weeks ( $P < 0.01$ ), with a mean percentage reduction of 68.84%. P-NRS had a mean value of 8.9  $\pm$  1.6 at baseline vs. 2.5  $\pm$  2.4 at 16 weeks ( $P < 0.01$ ; mean percentage reduction of 71.91%). The mean S-NRS also showed a significant reduction from baseline to timepoint (7.8  $\pm$  1.8 at baseline vs. 3.3  $\pm$  2.9 at week 16;  $P < 0.05$ ; mean percentage reduction of 57.69%). As for quality of life, DLQI score at baseline was 18.4  $\pm$  4.7 vs. 7.65  $\pm$  6.4 at 16 weeks ( $P < 0.01$ ; mean percentage reduction of 58.42%). No significant differences in the response to the treatment with dupilumab were found among the various phenotypes of AD. A similar improvement of all the parameters analysed was also found for the group of patients aged 18–64 years. Indeed, in younger subjects EASI reduced from 30.30  $\pm$  4.58 to 6.83  $\pm$  3.90 ( $P < 0.01$ ; mean percentage reduction: 77.45%), P-NRS from 8.47  $\pm$  0.79 to 2.80  $\pm$  1.14 ( $P < .01$ ; mean percentage reduction: 66.94%), S-NRS from 7.62  $\pm$  1.03 to 2.10  $\pm$  1.28 ( $P < 0.01$ ; mean percentage reduction: 72.44%), and DLQI from 17.70  $\pm$  3.85 to 4.85  $\pm$  2.36 ( $P < 0.01$ ; mean percentage reduction: 72.50%). No statistically significant differences between the two groups of patients were recorded regarding EASI, N-NRS, P-NRS and DLQI percentage reduction (Fig. 2).

Eosinophilia ( $>500$  eosinophils/ $\text{mm}^3$ ) was detected in 7.91% (20/253) of patients at baseline and in 15.02% (38/253) at week 16 ( $P < 0.05$ ). At baseline, total IgE levels were above the normal range in 121/253 (47.83%) patients. In these subjects, the mean value of 2532  $\times 10^3$  IU/L and decreased in 62/121 (51.24%) patients to a mean value of 1119  $\times 10^3$  IU/L at week 16 ( $P = 0.6$ ).

Topical corticosteroids (TCs) and/or topical immunomodulators [tacrolimus and pimecrolimus; (TIMs)] were used at



**Figure 1** Results describing improvement in terms of mean variation of EASI, P-NRS, S-NRS and DLQI from baseline to week 16 in 253 patients  $\geq 65$  years old treated with dupilumab. Mean values of Eczema Area and Severity Index (EASI), numerical rating score (NRS) and Dermatology Life Quality Index (DLQI) of study population before (W0) and after 16 weeks (W16) of dupilumab treatment. Statistical significance was assessed by unpaired Student's *t*-test: \* $P < 0.05$ ; \*\* $P < 0.01$ .



**Figure 2** Mean percentage of reduction of EASI, P-NRS, S-NRS and DLQI from baseline to week 16 in 253 patients  $\geq 65$  years old and in 2152 patients 18–64 years old, treated with dupilumab. Mean values of percentage reduction of Eczema Area and Severity Index (EASI), numerical rating score (NRS) and Dermatology Life Quality Index (DLQI) in  $\geq 65$  years and 18–64 years ( $< 65$  years) patients, before and after 16 weeks of dupilumab treatment. Statistical significance was assessed by unpaired Student's *t*-test: not significant (NS).

baseline by 40.32% (102/253) and 32.02% (81/253) patients, respectively. Out of them, after 16 weeks of treatment, TCs dropped out by 58.82% (60/102;  $P < 0.01$ ) of patients, while TIMs were stopped by 13.58% (11/81;  $P = 0.285$ ) of patients. Systemic immunosuppressive treatments (CsA and MTX) were used in 91/253 (35.97%) patients at baseline. In our cohort, 80 of 253 (31.62%) patients had discontinued systemic immunosuppressive treatment at the start of dupilumab treatment, while 11 of 253 (4.35%) continued to receive systemic immunosuppressant drugs during dupilumab treatment. However, due to the improvement of AD, these drugs were stopped in all these patients during the 16 weeks of treatment with dupilumab; in none of them, a relapse of the disease was recorded.

### Safety profile

Sixty-one out of 276 (22.51%) patients experienced at least one AE during the 16-week treatment. Among our study population of 276 elderly AD patients, 8 (2.90%) were diagnosed with conjunctivitis at baseline, while 11 (3.99%) subjects were diagnosed with dupilumab-associated conjunctivitis during observation period. Conjunctivitis was mostly treated with artificial tears or hyaluronic acid eye drops. A pharmacologic topical approach with steroids, CsA or tacrolimus was required in 36.84% (7/19)

of cases. None of the 8 patients with pre-existent conjunctivitis significantly worsened during dupilumab treatment. Other common AEs were flushing (10/276; 3.62%), injection-site reaction (8/276; 2.90%), fatigue (8/276; 2.90%), headache (2/276; 0.72%), arthralgia (3/276; 1.09%) and generalized lymphadenomegaly (2/276; 0.72%). Only 1 (0.36%) patient discontinued the drug due to AE (lymphadenomegaly). One (0.36%) patient died for a cause not related to the treatment or to AD.

As far as the group of 18–64 years patients is concerned, the overall incidence of AEs during the 16-week treatment phase was 15.61% (336/2152 patients). The most common AE (incidence rate  $\geq 1\%$ ) was conjunctivitis (185/2152; 8.6%), followed by injection-site reaction (48/2152; 2.23%), fatigue (25/2152; 1.16%) and reactivation of oro-facial herpes simplex (23/2152; 1.07%). Conjunctivitis led to discontinuation of dupilumab in five (0.23%) patients. No patients stopped taking dupilumab for other AEs than conjunctivitis.

### Discussion

Atopic dermatitis in the elderly is increasing in industrialized countries, also following ageing of the general population.<sup>13</sup> Diagnosis is difficult, since elderly individuals often have pruritic skin disorders, e.g. asteatotic dermatitis, senile pruritus, uraemic



pruritus or adverse drug reaction.<sup>14</sup> Management is often complicated by the presence of comorbidities or daily intake of several drugs, making it difficult to administer traditional immunosuppressive drugs.<sup>9,10</sup> Few AD studies have assessed elderly atopic patients separately from other age groups, reporting differences in disease manifestations and management.<sup>1,4,15</sup> In our study, the percentage of elderly patients among those treated with dupilumab in 27 referral centres in Italy was 11.37%, thus confirming that AD is not rare also in subjects aged  $\geq 65$  years.<sup>1,15</sup> Proportion of adult-onset AD among these patients was of 74.28%; this percentage is about two- to threefold higher than the one reported in literature for adults in general.<sup>16,17</sup> In our study group of 276 patients, flexural dermatitis was the most frequent phenotype (45.28%). In 63/276 (22.82%), we found more than one phenotype, head/neck or hands eczema being the most frequent association. These findings were of both persistent and adult-onset AD. Previous studies reported that adult-onset AD seems to be associated with a higher probability of involvement of head/neck and hands, nummular eczema and lower probability of flexural lesions.<sup>17,18</sup> Our data concerning flexural and nummular eczema phenotype suggest significant differences with data reported by these other studies. Indeed, in our group of patients flexural was the most frequent clinical phenotype affecting 45.28% subjects, while nummular eczema was observed in only 7.25% of our elderly patients, without any significant difference between persistent or adult-onset group. Conversely, the second most common phenotype observed in our study was prurigo nodularis (24.28%) especially in adult-onset AD (86.57% of all prurigo nodularis patients). These differences in the frequency of clinical phenotypes may be due to epidemiological, genetic and environmental differences, all factors frequently encountered in the disease.<sup>19,20</sup> For example, it is known that Asian AD phenotype differs from the European American AD phenotype by demonstrating increased Th17 polarization in addition to Th2 skewing.<sup>21</sup>

Regarding dupilumab therapy, a significant improvement and a good safety profile were observed in 253 elderly AD patients in a real-world setting over a 16-week treatment period, as shown by a significant reduction of all of the disease severity scores that have been evaluated (EASI, pruritus-NRS and sleep-NRS, DLQI; Fig. 1). In our real-life cohort, 68.84% reduction of the mean EASI score was achieved at week 16 compared to baseline. This percentage is higher than those reported in the registration studies (51% and 44% in SOLO1 and SOLO2<sup>22</sup>, 69% in CHRONOS<sup>23</sup>, respectively, and 62.6% in CAFÉ<sup>12</sup> studies). Only 6.52% of the whole group of 276 elderly patients treated with dupilumab dropped out due to inefficacy of the drug before the week 16 (on average at week 12). Data from literature report that patients with initial unsatisfactory response to dupilumab may subsequently improve by continuing the treatment beyond

16 weeks.<sup>23–25</sup> Furthermore, the effectiveness of dupilumab in elderly patients was in line with the outcomes observed in younger population from the same geographical area.

In line with other real-life studies,<sup>11,25,26</sup> concomitant treatment with topical anti-inflammatory agents was a common practice in the real-life dermatological setting, although there has been a reduction in the use of topical therapy. Indeed, from baseline to week 16, TCs and TIMs were stopped in 58% and 13.6% of patients, respectively. At 16 weeks, none of the patients underwent systemic therapy for AD associated with dupilumab, thus confirming the effectiveness of this treatment. It should also be noted that in our patients dupilumab markedly improved key symptoms in AD, thus positively influencing their quality of life. Indeed, the mean P-NRS, S-NRS and DLQI score reduction was of 71.9%, 57.6% and 58.4%, respectively. According to previous studies, in our patient cohort the improvement in signs and symptoms was associated with a decrease of total serum IgE,<sup>11,25–27</sup> whereas eosinophil count did not change significantly between baseline and week 16 of follow-up.<sup>12,22,23</sup>

In our experience, dupilumab has proven to be a safe drug in the elderly, to an apparently lesser extent with an overall safety profile like that found in younger patients. Conjunctivitis was confirmed to be the most frequent AE, affecting 3.9% of our elderly patients, but to a lesser extent than the 18- to 64-year-old population (8.6%). Furthermore, this percentage is lower than that reported by in both clinical trials (range 5–28%)<sup>12,22,23</sup> and real-life studies (range 8–62%).<sup>10,26,28</sup> It should be noted that a quite frequently (10/276; 3.6%) reported AE was flushing, which is only rarely described in literature<sup>2</sup> as occurring in association with alcohol intake, due to a possible competitive inhibition of cytochrome P450 2E1 by dupilumab and ethanol.<sup>29</sup> In our study, the association between flushing and alcohol intake was reported by two of the 10 patients reporting this AE; therefore, in the remaining 8, the reaction is currently unexplainable; it could also be assumed that these patients did not pay attention to correlating alcohol intake with the onset of flushing. Furthermore, we emphasize that only 1/276 (0.36%) patient discontinued dupilumab due to an AE (lymphadenopathy).<sup>24</sup> while 5/2152 (0.23%) patients of 18- to 64-year group stopped taking the drug, due to conjunctivitis.

The strengths of this real-life study are that patients were not selected as in clinical trials and represented the largest sample ( $n = 276$ ) of elderly patients treated with dupilumab published in English literature, at the best of our knowledge. Indeed, of the 1472 patients with AD exposed to dupilumab in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, only 67 were over 65 years. Although in these trials, no differences in safety or efficacy were observed between older and younger adult AD patients, the number of patients aged 65 and over was not sufficient to draw robust conclusions.<sup>12,22,23</sup> Other rare reports in the literature on the topic refer to groups comprising few patients.<sup>4</sup> Limitations of this study include the retrospective

nature of the study and the short follow-up period. Longer-term observational studies should further confirm efficacy and safety of dupilumab in elderly atopic patients.

## References

- Williamson S, Merritt J, De Benedetto A. Atopic dermatitis in the elderly: a review of clinical and pathophysiological hallmarks. *Br J Dermatol* 2020; **182**: 47–54.
- Katsarou A, Armenaka M. Atopic dermatitis in older patients: particular points. *J Eur Acad Dermatol Venereol* 2011; **25**: 12–18.
- Chello C, Carnicelli G, Sernicola A *et al.* Atopic dermatitis in the elderly Caucasian population: diagnostic clinical criteria and review of the literature. *Int J Dermatol* 2020; **59**: 716–721.
- Napolitano M, Fabbrocini G, Scalvenzi M, Blasio C, Stingeni L, Patruno C. Efficacy and safety of dupilumab in atopic dermatitis in elderly patients: a retrospective study. *Clin Exp Dermatol* 2020; **45**: 888–890.
- Ramos-e-Silva M, Boza JC, Cestari TF. Effects of age (neonates and elderly) on skin barrier function. *Clin Dermatol* 2012; **30**: 274–276.
- Bieber T, D'Erme AM, Akdis CA *et al.* Clinical phenotypes and endophenotypes of atopic dermatitis: where are we, and where should we go? *J Allergy Clin Immunol* 2017; **139**: S58–S64.
- Tanei R, Hasegawa Y. Atopic dermatitis in older adults: a viewpoint from geriatric dermatology. *Geriatr Gerontol Int* 2016; **16**: 75–86.
- Patruno C, Fabbrocini G, Napolitano M. Clinical phenotypes of atopic dermatitis of the adult. *G Ital Dermatol Venereol* 2020. <https://doi.org/10.23736/S0392-0488.20.06532-3> [Epub ahead of print].
- Calzavara Pinton P, Cristaudo A, Foti C *et al.* Diagnosis and management of moderate to severe adult atopic dermatitis: a Consensus by the Italian Society of Dermatology and Venereology (SIDeMaST), the Italian Association of Hospital Dermatologists (ADOI), the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC), and the Italian Society of Allergological, Environmental and Occupational Dermatology (SIDAPA). *G Ital Dermatol Venereol* 2018; **153**: 133–145.
- Damiani G, Calzavara-Pinton P, Stingeni L *et al.* Italian guidelines for therapy of atopic dermatitis-Adapted from consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis). *Dermatol Ther* 2019; **32**: e13121.
- Fargnoli MC, Esposito M, Ferrucci S *et al.* Real-life experience on effectiveness and safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis. *J Dermatolog Treat* 2019; 1–7. [Epub ahead of print].
- De Bruin-Weller M, Thaçi D, Smith CH *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**: 1083–1101.
- Tanei R, Hasegawa Y, Sawabe M. Abundant immunoglobulin E positive cells in skin lesions support an allergic etiology of atopic dermatitis in the elderly. *J Eur Acad Dermatol Venereol* 2013; **27**: 952–960.
- Tanei R. Atopic dermatitis in the elderly. *Inflamm Allergy Drug Targets* 2009; **8**: 3984–4404.
- Megna M, Patruno C, Balato A *et al.* An Italian multicentre study on adult atopic dermatitis: persistent versus adult-onset disease. *Arch Dermatol Res* 2017; **309**: 443–452.
- Nettis E, Pellacani G *et al.* A multicentric study on prevalence of clinical patterns and clinical phenotypes in adult atopic dermatitis. *J Investig Allergol Clin Immunol* 2020; **30**: 448–450.
- Silverberg JI, Vakharia PP, Chopra R, Sacotte R, Patel N, Immaneni S *et al.* Phenotypical differences of childhood- and adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract* 2018; **6**: 1306–1312.
- Son JH, Chung BY, Kim HO, Park CW. Clinical features of atopic dermatitis in adults are different according to onset. *J Korean Med Sci* 2017; **32**: 1360–1366.
- Ozkaya E. Adult-onset atopic dermatitis. *J Am Acad Dermatol* 2005; **52**: 579–582.
- Kanwar AJ, Narang T. Adult onset atopic dermatitis: under-recognized or under-reported? *Indian Dermatol Online J* 2013; **4**: 167–171.
- Noda S, Suárez-Fariñas M, Ungar B *et al.* The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol* 2015; **136**: 1254–1264.
- Simpson EL, Bieber T, Guttman-Yassky E *et al.* Two phase 3 trials of dupilumab versus placebo in AD. *N Engl J Med* 2016; **375**: 2335–2348.
- 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* 2017; **389**: 2287–2303.
- [https://www.ema.europa.eu/documents/product-information/dupixent-epar-product-information\\_en.pdf](https://www.ema.europa.eu/documents/product-information/dupixent-epar-product-information_en.pdf) (last accessed: 20 October 2020).
- Fargnoli MC, Esposito M, Ferrucci S *et al.* A 48-week update of a multicentre real-life experience of dupilumab in adult patients with moderate-to-severe atopic dermatitis. *J Dermatolog Treat* 2020; 1–4.
- Olesen CM, Holm JG, Nørreslet LB *et al.* Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral center. *J Eur Acad Dermatol Venereol* 2019; **33**: 1562–1568.
- Ribero S, Giura MT, Viola R *et al.* Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in adult cohort: a real-life Italian tertiary centre experience. *J Eur Acad Dermatol Venereol* 2020; **34**: e380–e383.
- Faiz S, Giovannelli J, Podevin C *et al.* Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. *J Am Acad Dermatol* 2019; **81**: 143–151.
- Igelman SJ, Na C, Simpson EL. Alcohol-induced facial flushing in a patient with atopic dermatitis treated with dupilumab. *JAAD Case Rep* 2020; **6**: 139–140.

## Appendix 1

Collaborators DADE study group: L. Angileri, T. Bianchelli, A. Borghi, C. Buligan, G. Calabrese, P. Calzavara Pinton, F. Caroppo, C. Chello, G. Dal Bello, G. Damiani, M.C. Fargnoli, M. Ferrillo, M. Galluzzo, N. Gori, G. Gualdi, K. Hansel, L. Macchia, M. Mariano, S.P. Nisticò, G. Pertusi, V. Piras, E. Provenzano, G.M. Ravaioli, S. Ribero, M. Romanelli, P. Romita, E. Tolino, C. Trifirò.