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DUPILUMAB THERAPY OF ATOPIC DERMATITIS OF THE ELDERLY: A MULTI-CENTRE, REAL-LIFE STUDY

Running title: Dupilumab for the treatment of atopic dermatitis of elderly

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Conflict of interest:

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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

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Abstract

Background

Treatment of moderate-to-severe atopic dermatitis in the elderly may ~~present some problems related~~ 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 is 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 ≥ 65 years and affected by severe AD. Their main clinical features were also examined.

Methods

Data of elderly patients with severe (EASI≥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 1 phenotype was found in 63/276 (22.82%) subjects. ~~Two hundred and fifty three (91.67%) patients completed the study~~ 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 ~~(0.36%) patient~~ discontinued dupilumab due to an adverse event.

Conclusions

~~Our data suggest that severe AD is not a rare occurrence among the elderly and that some particular phenotypes, such as prurigo nodularis, are frequent among them. Furthermore,~~ ~~t~~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.

Introduction

Atopic dermatitis (AD) is a chronic disease in which the genetic impairment of skin barrier function and abnormal immune response lead to a complex reaction to environmental factors.[1] The worldwide prevalence of AD increased two to three fold over the past 30 years,[2] with high prevalence in both children (15-30%) and adults (2-10%).[1,2] Few studies have described so far the clinical presentation and prevalence of AD in elderly patients (≥65 years).[3,4] 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.[5] Moreover, innate and adaptive immunity changes of ageing (so called inflammaging) show some overlap with hallmarks observed in AD.[1]

Eld AD has recently been coned a fourth separate group, presenting with high prevalence in both children (15–30%) and adults (2–10%)

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.[6,7] 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.[8] 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. [1,7] 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, symptoms assessment and exclusion of other conditions, including cutaneous T-cell lymphoma, allergic contact dermatitis, scabies, or adverse drug reactions are needed in this condition. [1,6,7]

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.[9,10] 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.[9] 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 contra-indications.[11] In one randomized controlled trial, dupilumab exhibited a similar favorable safety profile and efficacy in all age groups of patients, including the elderly.[12] One case-series study in real life confirmed this aspect.[4] The aim of this multicentre retrospective, observational, real-life study was to evaluate the clinical features of AD patients aged ≥ 65 years and the potential benefit and safety of dupilumab in an Italian population.

Methods

Data of elderly (age ≥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: age ≥65 years, diagnosis of AD made by an expert, board-certified dermatologist; Eczema Area and Severity Index (EASI)≥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: 0–150 × 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±19.70 years (range18-91)] had been treated with dupilumab during the reference period. Of these, 2152 patients (1204 males; mean age 39.64±10.23) were aged 18-64 years and 276 patients (11.37%; 159 males) >65 years ~~with a~~ (mean age ~~of~~ 73.06±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<.01), with an average duration of the disease of 18.4 ± 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± 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.

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 ~~O~~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 weeks treatment. The other reasons of drop-out were patient choice (3; 1.09%), generalized lymphoadenomegaly (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±8.7 and significantly reduced to 9.1± 6.3 at 16 weeks (p-<-.01), with a mean percentage reduction of 68.84%. P-NRS had a mean value of 8.9±1.6 at baseline *vs* 2.5±2.4 at 16 weeks (p<.01; mean percentage reduction of 71.91%). The mean S-NRS also showed a significant reduction from baseline to timepoint (7.8 ± 1.8 at baseline *vs* 3.3 ± 2.9 at week 16; p < .05; mean percentage reduction of 57.69%). As for quality of

life, DLQI score at baseline was 18.4±4.7 *vs* 7.65±6.4 at 16 weeks (p–<–.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±4.58 to 6.83±3.90 (p<.01; mean percentage reduction: 77.45%), P-NRS from 8.47±0.79 to 2.80±1.14 (p<.01; mean percentage reduction: 66.94%), S-NRS from 7.62±1.03 to 2.10±1.28(p<.01; mean percentage reduction: 72.44%), and DLQI from 17.70±3.85 to 4.85±2.36 (p<.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 (Figure 2).

Eosinophilia (> 500 eosinophils /mm^3) was detected in 7.91% (20/253) of patients at baseline and in 15,02% (38/253) at week 16 (p<.05). At baseline, total IgE levels were above the normal range in 121/253 (47.83%) patients. In these subjects the mean value of 2532×10^3 IU/L and decreased in 62/121 (51.24%) patients to a mean value of 1119×10^3 IU/L at week 16 (p=.6).

Topical corticosteroids (TCs) and/or topical immunomodulators [tacrolimus and pimecrolimus; (TIMs)] were used at 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<.01) of patients, while TIMs were stopped by 13.58% (11/81; p=.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 lymphoadenomegaly (2/276; 0.72%). Only 1 (0.36%) patient discontinued the drug due to AE (lymphoadenomegaly). 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 ≥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 5 (0.23%) patients. No patients stopped taking dupilumab for other AEs than conjunctivitis.

Discussion

Atopic matitis (AD) in the elde-ly is gradually increasing in industrialized countries in association with the aging of society

Atopic dermatitis (AD) in the elderly is gradually increasing in industrialized countries in association with the aging of society

AD in the elderly is increasing in industrialized countries, also following ageing of the general population.[13] Diagnosis is difficult, since elderly individuals often have pruritic skin disorders, e.g. asteatotic dermatitis, senile pruritus, uremic pruritus, or adverse drug reaction.[14] Management is often complicated by the presence of comorbidities or daily intake of several drugs, making it difficult to administer traditional immunosuppressive drugs.[9,10] Few AD studies have assessed elderly atopic patients separately from other age groups, reporting differences in disease manifestations and management.[1,4,15] In our study, the ~~prevalence~~ percentage of elderly patients among those treated with dupilumab in 27 referral centres in Italy ~~is~~ was 11.37%, thus confirming that AD is not rare also in subjects aged ≥65 years.[1,15] Proportion of adult-onset AD among these patients was of 74.28%, this percentage is about two to three folds higher than the one reported in literature for adults in

general.[16,17] 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 seem to be associated with a higher probability of –involvement of head/neck and hands, nummular eczema, and lower probability of flexural lesions.[17,18] 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.[19,20] 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.[21]

Regarding dupilumab therapy, a significant improvement and a good safety profile was 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) (figure 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[22], 69% in CHRONOS[23], respectively, and 62.6% in CAFÉ[12] studies)-.[5] 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.[23,24,26,] 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,[11,25,26] 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 ~~TCsand~~ 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, [11,25-27] whereas eosinophil count did not change significantly between baseline and week 16 of follow-up. [12,22, 23]

In our experience, dupilumab has proven to be a safe drug ~~even~~ in the elderly, to an apparently lesser extent with an overall safety profile like that found in younger patients. ~~Indeed,~~ ~~e~~Conjunctivitis was confirmed to be the most frequent AE~~.~~, ~~-~~affecting 3.9% of our elderly patients, but to a lesser extent than the 18-64 year-old population (8.6%). ~~Still~~ Furthermore, this percentage is lower than that reported by in both clinical trials (range 5%-28%)[12,22,23] and ~~in~~ real-~~-~~life studies (range 8%-62%). [10,25,28] It should be noted that a quite frequently (10/276; 3.6%) ~~observed~~ reported AE was flushing, which is only rarely ~~reported~~ described in literature [2] as occurring in association with alcohol intake, due to a possible competitive inhibition of cytochrome P450 2E1 by dupilumab and ethanol.[29] In our study, the association between flushing and alcohol intake was reported by 2 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)~~.~~.[24] while 5/2152 (0.23%) patients of 18-64 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 1,472 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 atopic dermatitis patients, the number of patients aged 65 and over was not sufficient to draw robust conclusions.[12,22,23] Other rare reports in the literature on the topic refer to groups comprising few patients.[4] Limitations of this study include the retrospective nature of the study and the short follow-up period. Longer terms observational studies should further confirm efficacy and safety of dupilumab in elderly atopic patients.

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Table 1. Demographic and clinical baseline characteristics of AD elderly (≥65 years) patients treated with dupilumab (n=276)

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 ≥65 year-old treated with dupilumab

Mean values of EASI (Eczema Area and Severity Index), NRS (Numerical Rating Score), and DLQI (Dermatology Life quality Index) 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 ≥65 year-old and in 2152 patients 18-64 year-old, treated with dupilumab

Mean values of percentage reduction of EASI (Eczema Area and Severity Index), NRS (Numerical Rating Score), and DLQI (Dermatology Life quality Index) in ≥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)

Table 1. Demographic and clinical baseline characteristics of AD elderly (≥65 years) patients treated with dupilumab (n=276)

Variable	Value n (%)
Age (y)	73.06±6.83
Sex, male	159 (57.61)
Duration of AD (y)	18.4 ± 19.8
AD pattern	
Persistent	71 (25.72)
Late onset (≥18y)	205 (74.28)
AD phenotype	
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)
Clinical scores	
EASI score	29.2±8.7
Peak score on NRS for pruritus	8.9±1.6

Peak score on NRS for sleep	7.8 ± 1.8
DLQI score	18.4±4.7
Atopic comorbidities	
Rhinitis	47 (17.03)
Asthma	35 (12.68)
Conjunctivitis	35 (12.68)
Food Allergy	10 (3.62)
Other comorbidities	
Hypertension and cardiovascular disorders	121 (43.84)
Diabetes	43 (15.58)
Chronic kidney ~~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)
Previous systemic treatments for AD	
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; EASI: Eczema Area and Severity Index; NRS: numerical rating score; DLQI: Dermatology Life quality Index.