Therapeutic Impact and Management of Persistent Head and Neck Atopic Dermatitis in Dupilumab-Treated Patients

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Short title: Head/neck AD lesions affects dupilumab response

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Abstract

Background: Localization of atopic dermatitis (AD) in exposed areas such as hands, head, and neck has been considered as negative factor impacting on dupilumab response, though a comparison of exposed versus unexposed areas is not currently available.

Objectives: The aim of this study is to evaluate clinical response to dupilumab depending on the presence or persistency of AD skin manifestations in specific body areas.

Methods: The study retrospectively collected clinical and demographic data of adult patients affected by moderate to severe AD. Based on anatomical sites involved, 5 subcohorts of patients were identified.

Results: A total of 41 patients was included in the study. Disease amelioration was detected during the study period, though baseline head/neck and hand localization was associated with significant lower likelihood to achieve EASI≤1. In addition, patients with head/neck persistency showed significantly lower response when compared to patients without persistency of head/neck AD in terms of both mean EASI and DLQI reduction.

Conclusion: AD localization in exposed areas at the baseline and AD persistency at head/neck may have a negative impact on certain treatment response parameters to dupilumab therapy.

Introduction

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases with a prevalence in adults ranging from 7% to 10% in developed countries [1]. It is clinically characterized by intense itch and recurrent eczematous skin lesions occurring in different anatomical regions with frequent involvement of exposed areas such as head, neck and hands [2].

The approval of dupilumab, a fully human monoclonal antibody targeting the receptor α subunit constituting both IL-4 and IL-13 receptors, expanded the therapeutic armamentarium for moderate-severe AD that was essentially based on the use of systemic immunosuppressants including corticosteroids, cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine, whose long-term, continuous use might be burdened by organ toxicity [3,4]. Dupilumab is associated with high efficacy in controlling both symptoms and skin manifestations, along with an excellent safety profile [5]. The effectiveness of dupilumab in monotherapy was largely demonstrated in various real-world studies that confirmed outcomes deriving from clinical trials [6-12]. Nevertheless, exposed areas such as hands, head, and neck have been associated with an enhanced susceptibility to contact irritants and allergens, and the localization of AD in these areas is likely to predispose to a lower response to standard treatments [13-14]. Clinical response to dupilumab across 4 phase III trials was equally detected in different anatomical regions, though real-world data suggested that diverse morphology and distribution of AD lesions might affect the therapeutic response to dupilumab [13-15]. However, a comparison of dupilumab effectiveness in the treatment of exposed or unexposed areas is not currently available. The aim of this study is to evaluate clinical response to dupilumab depending on the presence or persistency of AD skin manifestations in specific body areas.

Materials and Methods

This retrospective study included adult patients affected by moderate to severe AD (EASI≥16) [16], referring to the dermatology outpatient clinic at the Fondazione Policlinico Universitario A. Gemelli, Rome, Italy, from April 2018 to November 2020, and under treatment with dupilumab for at least 16 weeks. All patients were encouraged to use emollients daily, while topical corticosteroids or topical calcineurin inhibitors were applied during the course of the study as needed. The following clinical and demographic data were collected from patient charts: sex, age, height, weight, BMI, personal history of AD or/and other atopic manifestation, age at AD onset, clinical phenotypes [12], topographical distribution of skin lesions, disease duration, comorbidities, previous and current therapies. Based on anatomical sites involved (head/neck, hand, genitalia, trunk, extremities), 5 subcohorts of patients were identified. Visits were performed at baseline, at week 4, week 16, and every 16 weeks thereafter. At each timepoint after baseline, the presence of AD lesions (EASI >0) was defined as persistency. In patients with a suspected overlapping allergic contact dermatitis (ACD) or airborne dermatitis, allergology consultation was requested. Additional diagnostic tests (such as patch tests [SIDAPA standard series] [17], prick tests, total and specific IgE concentrations) for contact allergens or aeroallergens were planned, according to allergist suggestion.

Disease severity was assessed by: a) Eczema Area Severity Index (EASI) varying from 0 to 72; b) itch Numeric Rating Scale (itch-NRS) ranging from 0 to 10; c) sleeplessness Numeric Rating Scale (sleep-NRS) with values 0-10; and d) Dermatology Life Quality Index (DLQI) varying from 0 to 30. Patients affected by prurigo nodularis were excluded as the objective outcome measures (EASI, IGA) cannot be applied to this clinical variant of AD [18].

Safety was assessed by incidence of treatment-emergent adverse events (TEAEs), objective examinations and laboratory tests (i.e., CBC, transaminases, creatinine, blood glucose, total serum IgE). This study was approved by the local ethical committee (Prot. N. 0046558/20).

2.1 Statistical analyses

Categorical variables were reported as frequencies and percentages while continuous variables were reported as mean and Standard Deviation (±SD) or median and interquartile range (IQR). The t test was used to compare paired values of absolute EASI, DLQI, sleep-NRS, itch-NRS scores between baseline, week 16 and week 32 among overall population, and to compare unpaired value of absolute EASI, DLQI, sleep-NRS, itch-NRS scores between patients with persistent and not persistent hand/head/neck eczema at week 16 and

week 32. Different endpoints of response were considered: absolute EASI ≤1 achievement according to a recent publication indicating the achievement of EASI value as optimal response to dupilumab treatment [19], 50%, 75% or 90% reduction of EASI from baseline at different time-points (EASI75 and EASI 90), DLQI improvement >4 points, itch-NRS score improvement >4 points, sleep-NRS score improvement >4 points.

Fisher exact test was performed to assess the association between response variable (EASI≤1 achievement, EASI50, EASI75, EASI90, >4-point improvement of DLQI, itch-NRS, and sleep-NRS) and the following factors: sex; pattern of AD (dichotomised as late onset and early onset); disease course (persistent/relapsing), main AD phenotype (persistent, erythrodermic, eczematous), disease duration (<10, 10-30, >30 years), presence/absence of allergic comorbidities (asthma/rhinitis/conjunctivitis), AD localization prior to treatment initiation (head/neck, hand, genitalia, trunk, extremities) and presence of AD lesions in specific anatomical sites during dupilumab therapy. Clinical variables were analyzed using the "as observed analysis" to handle missing data.

Linear regression analysis was performed to determine the association between two continuous variables: absolute DLQI (as the independent variable x) and absolute EASI (as the dependent variable y) values at week 16 during dupilumab treatment.

Associations and differences were considered statistically significant with a p value <0.05.

All comparisons and descriptive statistics were computed using the statistical package SPSS software version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Therapeutic response to dupilumab in the overall study population

A total of 41 patients (26 male, 15 female; mean age: 54.8±17.6) with at least 16 weeks of treatment with dupilumab was included in the study. Baseline demographic and clinical data are summarized in Table 1.

Dupilumab resulted effective in obtaining a significant reduction of both physician- and patient-oriented outcome measures at each timepoint compared to baseline (Table2). Mean baseline EASI was 24.1 (±7.3) and significantly reduced to 10.5 (±7.4; $p<0.0001$) after 4 weeks of treatment, with a further reduction to 6.0 (±11.4) at week 16, and to 1.6 (±1.6) at week 32. EASI50, EASI75 and EASI90 responses were achieved by 29/41 (70.7%), 12/41 (29.3%) and 4/41 (9.8%) at week 4, and by 37/41 (90.2%), 30/41 (73.2%) and 18/41 (43.9%) patients at week 16, respectively. Further improvement of clinical response was observed at week 32, with EASI75 achieved by 34/36 (94.4%) and EASI90 by 25/36 (69.4%) patients. In those patients (n=4) not achieving EASI 50 at week 16, dupilumab therapy was interrupted because of disease relapse and subsequently treated with systemic corticosteroids (n=2) whereas topical corticosteroids were added in the other 2 cases with clinical benefits, obtaining, at the following timepoint, EASI 50 response.

This clinical improvement reflected a significant amelioration in mean itch-NRS, sleep-NRS, and DLQI scores detected throughout the study period (Table 2). QoL improvement resulted in a significantly lower mean value of DLQI scoring at week 4 (9.0 ±5.2) compared to baseline (17.9±3.8), with a further decrease to 4.5 (±6.4) at week 16, and 1.7 (±2.8) at week 32 ($p<0.0001$ for each time point; Table 2). No impact on QoL, defined by DLQI 0/1, was reported in 11/41 (26.8%) of patients at week 16 and in 24/36 (66.7%) patients at week 36. EASI positively correlated with the DLQI, identifying DLQI as highly significant predictor of absolute EASI after 16-week dupilumab therapy (R^2=0,7492, p=0.0001). The line of best fit (Y = 1,58*X - 1,16) identified for DLQI 0-1, an absolute EASI≤1. Furthermore, the mean absolute EASI for patients achieving DLQI 0-1 was 0.8 (SD=1.1-95%CI=0,1-1,5). In addition, a progressive increase of patients with mild or absent disease (EASI≤1) was observed at different time points: 4/41 (9.7%) of patients at week 4, while 14/41 (34.1%) and 17/36 (47.2%) of patients reached EASI ≤1, at week 16 and 32, respectively.

Baseline factors predicting therapeutic response as absolute EASI≤1 likelihood achieved at week 16

We sought to define predictive baseline factors (affected body sites, gender, disease pattern, atopic comorbidities, disease duration) influencing treatment response, in particular the likelihood to obtain a complete or almost complete response (EASI≤1; Figure 1).

Baseline head/neck localization was associated with a significant lower likelihood to achieve EASI≤1 [OR: 0.19 (0.05-0.78) (p=0.023)], whereas no significant association was detected between baseline head/neck localization and the achievement of both EASI75 and EASI90 response. In addition, baseline hand localization was also associated with a lower likelihood to achieve EASI≤1 (OR: 0.18 [0.03-0.96], p<0.05), whereas other factors were not found to be significantly associated to a lower response (Fig. 2).

Persistent head and neck eczema during dupilumab treatment

Clinical response to dupilumab treatment was further investigated considering the persistency of AD lesions in different anatomical areas during dupilumab therapy. We observed a decrease of all severity scores throughout the observation period when compared to baseline values, independent of the persistency of AD lesions in any single anatomical site (data not shown). Nevertheless, patients with head/neck persistency showed significantly lower response when compared to patients without head/neck persistency of AD in terms of both mean EASI and DLQI reduction (Table 3). Conversely to the head/neck localization, persistency in other body areas was not significantly associated with a lower response to dupilumab therapy (data not shown). Subjects with head/neck AD involvement at baseline were 25/41 (61%), while residual eczematous lesions in this area were detected in 18/41 (43.9%) at week 4, 17/41 (41.5%) at week 16, and 4/27 (14.8%) at week 32. Mean EASI at the baseline was similar between patients having residual head/neck AD, compared to patients without h/n persistency [24.8 (±8.0) and 23.0 (±6.0)] and dampened over time in both subcohorts, though mean EASI resulted significantly lower in patients without persistent head/neck eczema, at week 16 [3.4 (±4.5) and 9.9 (±16.5); p=0.03] and week 32 [1.4(±1.3) and 2.9 (±1.7), p=0,01]. No difference in terms of EASI 50, EASI75, and EASI90 responses was observed comparing the 2 patient subcohorts. Similar to mean EASI, a significant improvement in DLQI was observed between subjects with or without persistent head/neck AD at week 16, whereas the amelioration of itch and sleep disturbances was greater but not significant in patients without head/neck eczema (Table 3).

Comprehensive patch testing, comprising SIDAPA standard series with the addiction of advanced series according to the patient's personal history, were performed in 17 patients with persistent head/neck AD, in 9/17 (52.9%) patients the test resulted negative, 6/17 (35.3%) cases resulted positive to nickel sulphate, 2/17 (11.8%) cases were positive to cobalt chloride, and 1/17 (5.8%) showed positivity respectively to potassium dichromate, colophony, disperse blue 106, and hydrocortisone acetate. Prick tests were performed in 4 patients

with persistent h/n AD and in all cases allergy tests resulted positive for common aeroallergen: Dermatophagoides pteronyssinus and farinae in 4/4 (100%) cases, graminacee mix in 3/4 (75%), cypress in 3/4 (75%), parietaria in 3/4 (75%) , olive in 2/4 (50%), cat fur in 2/4 (50%), cat dander in 1/4 (25%), absinthe in 1/4 (25%).

Allergen avoidance, wherever applicable, did not obtain any significant clinical benefit in these patients

Malassezia-specific IgE resulted positive in 5/10 patients affected by persistent h/n AD; in those patients an 8-week combination with 200 mg itraconazole (fluconazole) daily and topical resulted ineffective or slightly effective in improving AD manifestations/lesions.

In patients with residual AD of head/neck, a topical therapy (corticosteroids and/or calcineurin inhibitors) was associated to dupilumab in 27 cases while systemic immunosuppressants (namely corticosteroids, cyclosporine or methotrexate) were added in 6 cases. In general, topical low-to-mid potency corticosteroids were preferred for treating acute flares, whereas maintenance therapy was frequently performed using pimecrolimus cream. As combination therapy, systemic agents were selected based on the severity of disease, presence of comorbid conditions and concomitant co-medications. In five out of 6 patients treated with a systemic combination therapy, oral corticosteroids were added.

A significant reduction of signs and symptoms of AD was achieved by all patients who underwent combined therapy.

Adverse events and cause of interruption during dupilumab therapy

The most frequently observed AE was conjunctivitis with 8/41 (19.5%) events, all of them were mild or moderate, responding to topical corticosteroid-based compounds and obtaining resolution without dupilumab discontinuation in all cases. Other AE reported were alopecia areata in 3/41 (7.3%) patients, injection site reaction in 3/41 (7.3%) and herpes zoster in 2/41 (4.9%). Three of 41 (7.3%) patients interrupted treatment during the observation period for AD worsening.

Discussion

In this real-world study, we confirmed dupilumab effectiveness in treating moderate-severe AD, with response rates in terms of EASI75 and EASI90, that resulted higher compared to previous real-world studies (73.2% and 43.9% respectively at week 16), most likely due to the association with conventional systemic agents occurring in a consistent proportion of cases (17.1%) that could enhance dupilumab effectiveness [20].

Relevance of head/neck localization

Besides the overall evaluation of treatment response in patients with moderate-severe AD, this study aimed to analyze clinical response to dupilumab according to the affected body sites. A sub-analysis of four phase 3 dupilumab trials (SOLO 1, SOLO 2, CAFE' and CHRONOS) that considered four anatomical regions (trunk, head and neck, upper extremities and lower extremities) according to the EASI subdivision, revealed an equal activity of dupilumab in all body regions [15]. However, this subanalysis evaluated the percentage variation of EASI in selected body sites from baseline throughout the study period (i.e., EASI75 and EASI90), while residual AD in specific body sites, assessed by absolute EASI, was not analyzed.

Our study showed that dupilumab effectiveness, meant as the achievement of EASI 50, EASI75 and EASI90 response, was not affected by any clinical feature, including the persistency of AD in specific body sites. Improvements in sleep disturbances, pruritus, and QoL were reported in patients with or without head/neck involvement. However, head/neck localization at the baseline and persistency of AD lesions during dupilumab therapy was associated with a significantly lower response in terms of mean EASI and DLQI reduction compared to patients without persistency of AD lesions in head/neck.

Identification of therapeutic goals in AD and impact of head/neck AD on treatment response

Because the achievement of DLQI 0-1 was associated with an EASI ≤1 at week 16, we considered this therapeutic goal as clinically meaningful, though an international Steering Committee defined a treat-to-target strategy through an eDelphi process, indicating the achievement of EASI75 or EASI ≤7 as therapeutic target at 6 months [21]. In our study, baseline head/neck localization affected dupilumab response lowering the likelihood in achieving an EASI ≤1 at week 16, and, thus, DLQI 0-1. This negative impact of persistent head/neck AD on patients' QoL was suggested by a cross-sectional study reporting an association between face localization of AD lesions and patient-perceived importance of an

almost complete clearance [22]. Another real-life experience reported persistency of AD as significantly higher on the face compared to other body regions, with 21/48 (43.8%) of subjects continuing to manifest eczematous lesions on the face at the first follow up visits (on average 7.8 weeks) [23].

Diagnostic and therapeutic management of persistent head/neck AD

In the management of recalcitrant AD lesions, we sought to investigate eventual exposure to irritants and allergens causing an irritative and/or allergic contact dermatitis that might frequently overlap with AD, challenging the therapeutic management (Fig. 3) [14,24]. Notably, expanded patch tests resulted positive in 12 of 13 subjects with residual head and neck AD, and clinical amelioration was observed following allergen avoidance [23]. Thereby, AD persistency at head/neck was related to an allergen-induced dermatitis, suggesting comprehensive patch testing obtained integrating a basic panel like SIDAPA standard series to advanced series chosen according to patient's anamnesis can be useful for the therapeutic management. However, in our study patch tests positivity was detected in 8/17 (47%) of residual head and neck AD cases. Furthermore, we performed prick tests for common aeroallergens that resulted positive in 4/4 cases, but no clinical improvement was observed after avoidance of allergen exposure when applicable. We also considered other factors that could be implicated in AD head/neck manifestations, including the hypersensitivity to Malassezia yeast [14,25]. Interestingly, one study with 589 AD patients detected increased levels of Malassezia-specific IgE in all cases with head/neck AD involvement, compared to 18% of subjects without the affection of that body region [24]. In our study, Malassezia-specific IgE positivity was detected in 5/10 patients with recalcitrant head/neck AD but partial or no benefits were observed using antifungal therapies, consisting in itraconazole or fluconazole. Thereby, the diagnostic tests did not result therapeutically meaningful as marked beneficial effects derived only from combining immune-targeted therapies, both topical and systemic, to dupilumab treatment, in most cases of persistent head/neck AD.

The retrospective design of the study and the small sample size of patients included limit the analyses to the "as observed" method to handle missing data and data needs to be confirmed in larger patient cohorts.

Statement of Ethics: We confirm that all the subjects gave their written informed consent and the study protocol was reviewed and approved by Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore, Prot N.: 0046558/20

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Author contribution

All authors made substantial contribution to this manuscript, in details:

AC: Concept and design, analysis and interpretation of data, reviewed the article critically for important intellectual content

NG, GC, LC, CG, CC, CDS: patient management, drafted the article

LDN: performed statistical analysis of data with graphical and tabular conceptualization

CC, FA: acquisition of data

KP, CDS: reviewed the article critically for important intellectual content, gave final approval of the version to be published.

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Figure legends

Figure 1. EASI scoring correlated with DLQI. Linear regression determined the association between DLQI (as the independent variable x) and EASI (as the dependent variable y) absolute values at week 16 during dupilumab treatment.

Figure 2. Baseline factors affecting likelihood of achieving an absolute EASI≤1 at week 16.

Figure 3. Algorithm related to the management of head/neck AD persistency.