Facial and neck erythema associated with dupilumab treatment: A systematic review

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Background: Neither dupilumab-associated facial erythema nor neck erythema was reported in phase 3 clinical trials for the treatment of atopic dermatitis, but there have been a number of reports of patients developing this adverse event in clinical practice.

Objective: To outline all cases of reported dupilumab-associated facial or neck erythema to better characterize this adverse event, and identify potential etiologies and management strategies.

Methods: A search was conducted on EMBASE and PubMed databases. Two independent reviewers identified relevant studies for inclusion and performed data extraction.

Results: A total of 101 patients from 16 studies were reported to have dupilumab-associated facial or neck erythema. A total of 52 of 101 patients (52%) had baseline atopic dermatitis facial or neck involvement and 45 of 101 (45%) reported different cutaneous symptoms from preexisting atopic dermatitis, possibly suggesting a different etiology. Suggested etiologies included rosacea, allergic contact dermatitis, and head and neck dermatitis. Most commonly used treatments included topical corticosteroids, topical calcineurin inhibitors, and antifungal agents. In the 57 patients with data on the course of the adverse events, improvement was observed in 29, clearance in 4, no response in 16, and worsening in 8. A total of 11 of 101 patients (11%) discontinued dupilumab owing to this adverse event.

Limitations: Limited diagnostic testing, nonstandardized data collection and reporting across studies, and reliance on retrospective case reports and case series.

Conclusion: Some patients receiving dupilumab develop facial or neck erythema that differs from their usual atopic dermatitis symptoms. Prompt identification and empiric treatment may minimize distress and potential discontinuation of dupilumab owing to this adverse event. (J Am Acad Dermatol 2021;84:1339-47.)

Key words: alcohol-induced facial flushing; allergic contact dermatitis; dupilumab; facial erythema; facial flush; facial redness; head and neck dermatitis; rosacea.

INTRODUCTION

The most frequently reported adverse events with dupilumab for treatment of atopic dermatitis in phase 3 clinical trials were conjunctivitis, injection site reactions, and herpes infections.[1-3] Although not reported in randomized controlled trials, there have been increasing reports of erythematous eruptions on the face and neck associated with dupilumab use,

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with incidences of up to 10% in clinical practice.[4] Various terms have been used to describe this adverse event, including *new regional dermatoses*,[5] *dupilumab facial redness*,[4,6] *paradoxic head and neck erythema*,[7] and *persistent facial dermatitis*.[8,9]

Because involvement of visible areas such as the face and neck is known to have a greater influence on patient-perceived importance of almost complete or complete skin clearance in patients with atopic dermatitis,[10] facial and neck erythema are a barrier to achieving desired patient-centered treatment outcomes. Despite the importance of managing this adverse event, the etiology and pathogenesis remain unclear. In this systematic review, we aimed to summarize all published cases of facial or neck erythema associated with dupilumab for treatment of atopic dermatitis, summarize proposed etiologies, and review management strategies.

CAPSULE SUMMARY

- Dupilumab-associated facial or neck erythema has not been reported in clinical trials. Etiology and pathogenesis of this adverse event are poorly understood.
- Prompt identification and management of this adverse event is needed to minimize its negative influences and potential discontinuations. Different diagnoses that should be considered include rosacea, allergic contact dermatitis, and head and neck dermatitis.

METHODS

We registered a protocol to PROSPERO and used PRISMA reporting guidelines.[11] We searched PubMed and EMBASE databases from inception to June 3, 2020, using the following key terms: "dupilumab facial redness," "facial redness," "facial rash," "facial flush," "head and neck dermatitis," "periocular dermatitis," "allergic contact dermatitis," AND "dupilumab." In addition, we hand searched references of any relevant studies and review articles (Fig 1). We included studies reporting at least 1 patient who had developed facial erythema, neck erythema, or both during dupilumab treatment for atopic dermatitis. We excluded review articles, non-English articles, and reports of dupilumab treatment for conditions other than atopic dermatitis. Two reviewers (C.E.J. and A.F.) independently assessed the articles for inclusion. The same reviewers independently performed data extraction and conducted quality assessment using the tool described by Murad et al[12] for case reports and series. We extracted data on study type, patient demographics, baseline atopic dermatitis involvement, efficacy of dupilumab, clinical characteristics of the adverse event, management of adverse event and outcomes, and discontinuations. Any discrepancies between the 2 reviewers were resolved by a third reviewer (J.R.G.).

RESULTS

We included 16 studies with a total of 101 patients (mean age 39 years) (Table I, Fig 1).[4-9,13-22] Baseline atopic dermatitis on the face or neck was observed for 52 of 101 patients (52%). Average time to onset of facial or neck erythema after dupilumab initiation was 11 weeks. Ten cases were episodic, with 2 triggered by alcohol consumption[15,19] and 8 by dupilumab injections.[9,14,21] Symptoms other than erythema included scaling (n = 6), pruritus (n = 3), pain (n = 3), and burning sensation (n = 9). On physical examination, lesions were described as urticarial (n = 4), edematous (n = 2), lichenified (n = 2), and warm (n = 2). Almost half of patients (45/101) reported that symptoms were different from their typical atopic dermatitis.

Twenty-five patients underwent additional investigations, including patch testing (n = 8), biopsy (n = 14), immunohistochemical staining (n = 7), reflectance confocal microscopy (n = 6), and blood tests for antinuclear antibodies (n = 2), erythrocyte sedimentation rate (n = 2), and anti-*Malassezia*–specific immunoglobulin antibodies (n = 1) (Supplemental Table I available via Mendeley at https://doi.org/10.17632/thfvsf43y6.1). Commonly used treatments to manage facial or neck erythema were topical corticosteroids (n = 43), topical calcineurin inhibitors (n = 32), and topical and oral antifungals (n = 18). Of the 57 patients with data on the course of the adverse event, treatment resulted in clearance in 4, improvement in 29, no response in 16, and worsening in 8. Complete clearance was achieved by allergen avoidance in 1 case[8] and systemic antifungals in 3 cases.[6,16] Nine patients discontinued dupilumab owing to dissatisfaction with disease control because of facial or neck erythema, whereas 2 discontinued because of a combination of this adverse event plus another reason. Various etiologies for dupilumab-associated facial or neck erythema have been proposed, including rosacea and allergic contact dermatitis.

Overall, categories that assessed the causality of the adverse event received lower scores in the

Abbreviation used:

Th: T helper cell type

quality assessment of the case reports/series. Full risk of bias analysis is reported in Supplemental Table II.

PROPOSED ETIOLOGIES

Rosacea

Two of the 16 articles described dupilumab-induced rosacea as the most likely etiology of facial or neck erythema.[5,9] In the case report by Heibel et al,[9] the patient presented with follicular papules involving bilateral aspects of the cheeks and nose, with an episodic flaring pattern causing a burning sensation. With a presentation suggestive of rosacea, topical metronidazole was initiated, without effect. After discontinuation of dupilumab, the adverse event fully resolved.

Similarly, in the study by Zhu et al,[5] a patient presented with erythematous and eczematous lesions on the face. A biopsy was performed, the result of which was consistent with rosacea, dermatophytosis, and actinic keratosis. Improvement was observed in 45 days after initiation of topical terbinafine.

Dupilumab-mediated interleukin 4 and 13 initiation and subsequent suppression of the T helper cell type (Th) 2 pathway is thought to result in a Th1- and Th17-dominated response.[23] As a result, there have been increasing reports of patients developing Th1-mediated dermatoses such as psoriasis after dupilumab initiation.[23-27] This may explain the dupilumab-induced rosacea because its inflammatory response is understood to be primarily Th1 and Th17 driven.[28] Moreover, proliferation of demodex mites has been associated with Th2 impairment in mouse models,[29] and may contribute to the pathogenesis of dupilumab-induced rosacea.[30] An increased number of demodex mites has also been proposed as one of the explanations for increased incidences of conjunctivitis with dupilumab use.[31]

Alcohol-induced facial flushing

Alcohol-induced facial flushing is another pattern of facial or neck erythema that has been reported with dupilumab use. In one case report, a patient reported overheating, with sharply demarcated erythema of the face, neck, and décolleté 3 to 4 minutes after alcohol ingestion.[15] Likewise, in another case report, a patient developed periorbital and perioral erythema soon after drinking alcohol.[19] This occurred after 16 weeks of dupilumab treatment in the first case, and after the first injection in the second case. With alcohol-induced facial flushing being a known adverse event of tacrolimus use,[32] the authors initially considered this as a potential explanation owing to the second patient's history of tacrolimus use. However, this was thought to be less likely because the patient had been receiving tacrolimus daily for the past few years, without symptoms.[19]

The majority of alcohol-induced facial flushing occurs from an inherited deficiency of aldehyde dehydrogenase 2 enzyme in the East Asian population.[33,34] Although less common, acquired etiologies include tacrolimus use and use of hepatically metabolized medications, which can interfere with the degradation of alcohol.[32,35] As a monoclonal antibody, dupilumab is assumed to have minimal hepatic elimination. This has been confirmed through an open-label drug-drug interaction study examining the pharmacokinetics of 5 Cytochrome P450 substrates, which showed that dupilumab does not significantly affect Cytochrome P450 enzyme activities.[36]

Allergic contact dermatitis

The pathogenesis of allergic contact dermatitis is thought to involve allergen-dependent elicitation of Th1, Th2, and Th17. It has been proposed that dupilumab-induced interleukin 4 inhibition, resulting in Th1/Th17 polarization, may therefore worsen more Th1-dependent allergen responses while improving Th2-dominant allergen responses. This hypothesis may explain the conflicting reports of increased incidences of facial or neck erythema in patients with allergic contact dermatitis in one study,[37] whereas other studies show improvement of allergic contact dermatitis with dupilumab treatment.[38]

However, it remains unclear why the worsening of allergic contact dermatitis would be localized to the face and neck. In a case report by Suresh and Murase,[8] 2 patients with a history of positive allergen results on patch testing showed new positive results for allergens not previously identified: perfume and fragrance for one patient and limonene from shampoo for the second patient. Because these allergens are commonly found in products applied near the face and neck, these findings may explain the localization of allergic contact dermatitis to these regions. Moreover, the face has a relatively thin epidermis compared with other regions of the body, allowing easier permeation of allergens, which may contribute to the increased allergen hypersensitivity in these regions. Allergen avoidance

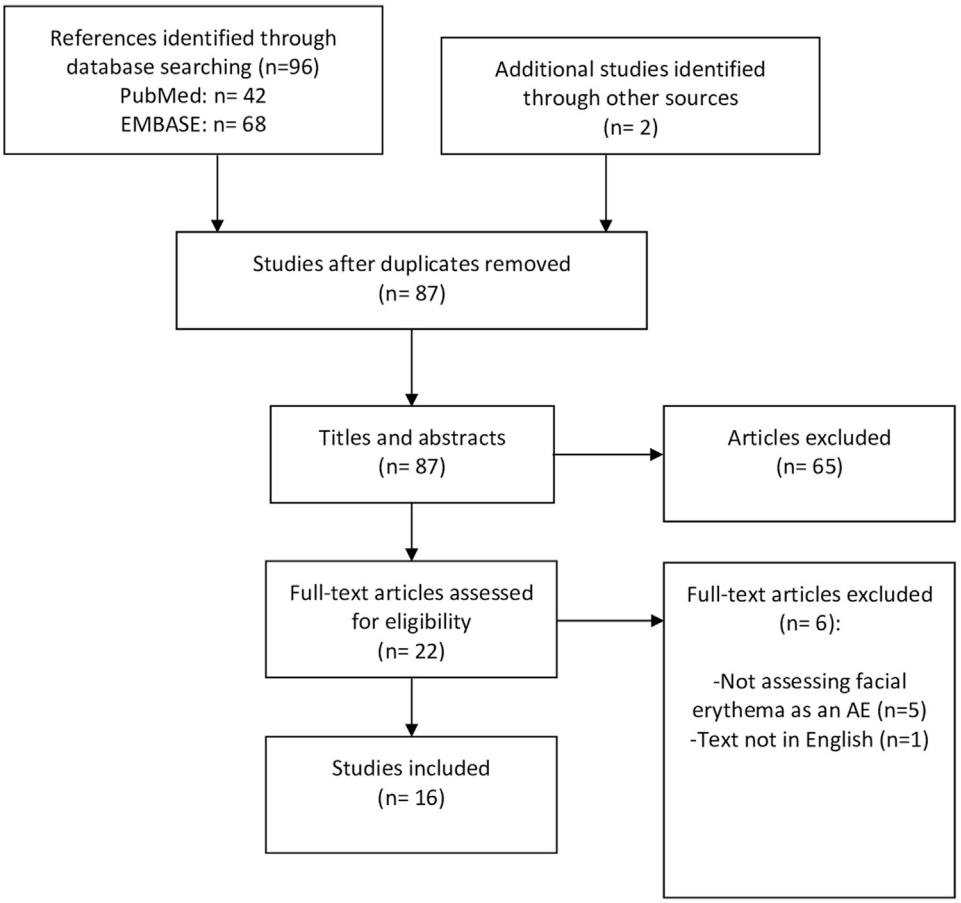

Fig 1. Selection process for study inclusion.

led to 75% improvement in one patient and clearance in the second patient.

Head and neck dermatitis

Soria et al[16] stated that 42 of 1000 patients in their registry who were treated with dupilumab for atopic dermatitis reported worsening of baseline head and neck dermatitis (n = 32) or new-onset head and neck dermatitis (n = 10). Topical agents that were used included tacrolimus (19/42), steroids (11/42), both tacrolimus and steroids (2/42), and antifungal agents (2/42). Four patients used systemic antifungals, with 2 experiencing complete regression. Overall, 22 of 42 patients had improvement of symptoms, 5 of 42 experienced persistent symptoms, 8 of 42 had worsening symptoms, and 5 of 42 discontinued owing to head and neck dermatitis.

In a case report by de Beer et al,[6] 2 patients developed erythematous and scaly plaques that were itchy and painful. Cutaneous involvement included the face and neck for the first patient and only the face for the second patient. Biopsy was performed in both patients, which revealed parakeratoses with numerous neutrophilic granulocytes, acanthosis, spongiosis, and infiltration of lymphocytes, neutrophils, and eosinophils in the upper dermis. For one patient, *Malassezia*-specific immunoglobulin E levels were tested and found to be elevated. Both patients were given oral itraconazole 200 mg once daily, which led to significant improvement for one patient and complete clearance by 3 weeks for the second one. Investigations and response to treatment supported head and neck dermatitis as the proposed etiology.

Malassezia furfur is a yeast that belongs in the normal skin flora. It is especially abundant in areas with concentrated sebaceous glands such as the head and neck.[39] Particularly in atopic dermatitis patients, because of the disrupted skin barrier function, *M furfur* easily penetrates the skin and initiates an inflammatory cascade to which *Malassezia*-specific immunoglobulin E is produced.[40] *Malassezia*-specific immunoglobulin E is a specific marker of head and neck dermatitis, shown to be elevated in 100% of patients with head and

Table I. Studies reporting facial erythema, neck erythema, or both with dupilumab use

Author (study type)	Demographic	Baseline regions affected	Onset of red face, signs and symptoms	Treatment and outcome
Dalia, 2018 (CR)	26 y, F	NA	6 mo, persistent worsening rash on face and neck	Topical calcipotriene, oxiconazole, ivermectin, clobetasol, tacrolimus, oral prednisone, fluconazole, doxycycline; unresponsive
Suresh, 2018 (CS)	1. 52 y, F 2. 54 y, F	1. Body, scalp, face 2. Chest, face, body	1. Residual dermatitis on forearms, neck, and face 2. Persistence of facial rash (red papules on the face)	1. Allergen avoidance; 75% improvement in 2.5 mo 2. Allergen avoidance; clearance
Albader, 2019 (CR)	28 y, F	Limbs, trunk	Painful, warm, erythematous, nonpruritic rash in the face and neck; 4 h after every injection, resolving after 2 d	Hydroxyzine and mometasone furoate cream BID for 3 d after injection; rash fading after 2 d
De Beer, 2019 (CR)	1. 39 y, M 2. 29 y, M	NA	1. 11 wk, worsening redness, scaling, pruritus and pain of erythematous and scaly plaques on head and neck 2. 6 mo, erythematous, and scaly plaques on face, itchy and painful	1. TCS, no response, oral itraconazole 200 mg once daily (total period of 1 mo); 1 wk f/u: significant improvement, third week f/u: clearance 2. TCS, topical ivermectin, no improvement Oral itraconazole 200 mg once daily, significant improvement
De Wijs, 2019 (CS)	6 M, 1 F (mean age 34.4 y)	6/7 head, neck	10–39 wk, gradual development of sharply demarcated patchy erythema in HN. 1/7 scaling, itch, and burning symptoms (itching and burning, different from preexisting), 1/7 scaling and burning	TCS (7/7), TCI (2/7), topical ivermectin (1/7), topical antibiotics (1/7), antihistamines (2/7), oral corticosteroids (2/7), systemic antibiotics (1/7), systemic antifungal medication (1/7); unresponsive
Heibel, 2019 (CR)	67 y, F	Face, neck, trunk, upper and lower extremities	3 mo, episodic flares, starting 2 d after injection and resolving day 12–13 postinjection. Significant increase in facial erythema, edema, pink follicular-based papules on nose and bilateral aspect of cheeks, mild burning	Metronidazole cream; no improvement Discontinuation of dupilumab owing to this AE and financial burden
Herz, 2019 (CR)	19 y, F	NA	4 mo, 3–4 min after drinking alcohol, flushing/overheated, sharply demarcated erythema of face, neck, décolleté; resolved after 30 min	NA
Soria, 2019 (CS)	26 M, 16 F, (mean age 38.6 y)	32/42 baseline HN involvement	65.4 d, exacerbation or new-onset HND	Topical: tacrolimus (19/42), TCS (11/42), both tacrolimus and TCS (2/42), antifungal (2/42), Systemic: antifungal (4/42) Outcomes: improvement (22/42), resolution (2/42), persistence (5/42), aggravation (8/42)
Wang, 2019 (CR)	40 y, M	NA	3 mo, violaceous erythematous patches distributed diffusely on the face with minimal scale	Oral-pulse fluconazole 150 mg weekly for 1 mo; no improvement. Mycophenolate mofetil 500 mg BID and topical mometasone 0.1% cream for 1 mo; no improvement. Discontinued dupilumab owing to persistent facial erythema and worsening AA

Continued

Table I. Cont'd

Author (study type)	Demographic	Baseline regions affected	Onset of red face, signs and symptoms	Treatment and outcome
Yamane, 2019 (CR)	1. 66 y, F 2. 28 y, F	1. Flexor surfaces of elbow, top of feet, hands, mouth, periocular involvement 2. Hand and upper extremity	1. 1 wk, severe periocular dermatitis with skin thickening and peeling (exacerbation of perioral AD); at 3 wk, periocular dermatitis extended to lateral aspect of temples and bridge of nose 2. 5.5 mo, flare of hands, arms, periocular dermatitis for the first time. Bilateral periocular- erythema, edema, bilateral upper and lower skin crease thickening. Fine, erythematous rash at lateral canthi and nose.	1. Dexamethasone/neomycin/polymyxin B drops QID, ointment BID; not effective. Oral azithromycin; not effective. Methylprednisolone 4 mg, 2 rounds. Topical tacrolimus BID, hydrocortisone 1% cream PRN for 5 wk; returned to baseline 2. Topical petroleum jelly, fluorometholone topical ointment daily; outcome NA. Discontinued after 15 dupilumab injections owing to this AE
Zhu, 2019 (CS)	9 F, 5 M (age range 20−60 y)	NA	Site: 12/14 only face, 1/14 face, neck, and chest, 1/14 face, trunk, and thighs Morphology: 10/14 erythematous, 1/14 urticarial, 3/14 both	TCS (8/14), TCI (3/14), topical terbinafine (1/14), topical metronidazole (1/14), crisaborole (1/14), mupirocin (1/14), bleach bath (1/14), antifungal (1/14), oral corticosteroid (1/14), dexamethasone (1/14) 3/14 discontinued owing to this AE
Igelman, 2020 (CR)	26 y, F	Face, neck, hands, scalp	Soon after starting dupilumab, periorbital and perioral erythema after drinking alcohol; resolved in 20 min regardless of continued alcohol intake. Reaction did not occur after every alcohol ingestion	NA
Waldman, 2020 (CS)	4 F, 7 M (age range <18−75) y	NA	NA	NA if given to patients, but states approach of treating with topical ketoconazole 2% cream BID for 2 wk and then to patch test nonresponders
Stout, 2019 (CS)	5 patients (age and sex NA)	All had generalized dermatitis	After 4−16 wk, 5 had persistent dermatitis localized to face, neck, or both. 1/5 facial dermatitis worsened with dupilumab, despite clearance on rest of body.	Midpotent to superpotent TCS with or without TCI; no improvement Allergen avoidance; result not available
Okiyama, 2020 (CR)	4 M (mean age 38.5 y)	EASI for head/neck: 3.75−4.75; excluding head/neck: 20.4−22.5	Erythema on forehead, eyebrows, nasolabial folds, cheeks, and lower jaw; excluding areas around the eyes	Mild-class TCS, tacrolimus; no improvement Topical ketoconazole cream BID for 2 mo; improvement of EASI for head/neck, closer to severity to rest of body
Quint, 2020 (CS)	6 patients (age and sex NA)	NA	New-onset rosacea like folliculitis. Episodic flares few days after dupilumab injections. Symptoms: erythema, flushes, papulopustules, burning sensation. 2 developed similar symptoms on the thoracic regions in addition to the face.	NA

AA, Alopecia areata; *AD*, atopic dermatitis; *AE*, adverse event; *ANA*, antinuclear antibodies; *BID*, twice a day; *BSA*, body surface area; *CR*, case report; *CS*, case series; *EASI*, Eczema Area and Severity Index; *ESR*, erythrocyte sedimentation rate; *F*, female patient; *f/u*, follow-up; *HN*, head and neck; *HND*, head and neck dermatitis; *M*, male patient; *NA*, not applicable; *PRN*, as needed; *QID*, 4 times a day; *TCI*, topical calcineurin inhibitor; *TCS*, topical corticosteroid.

neck dermatitis compared with 28% of atopic dermatitis patients without head and neck dermatitis.[41]

Although reaction to *M furfur* in head and neck dermatitis was largely seen as a Th2-driven condition, recent mouse models have shown that *Malassezia* selectively induces Th17-driven inflammation.[42] Therefore, patients receiving dupilumab may experience a fortified Th17 response induced by inhibition of Th2. This theory is in keeping with the improvement of facial erythema with antifungal agents and the localized involvement of this adverse event to the face and neck.

Distribution within the head and neck region

The specific distribution of the rash within the head and neck region is variable in published reports, and may be an important factor in distinguishing the likely etiology of the facial or neck erythema for a given patient. In the study by Heibel et al,[9] the eruptions involved the cheeks and nose, which is the classic distribution of rosacea. Head and neck dermatitis associated with *M furfur* typically involves the seborrheic regions of the face, including the eyelids, forehead, cheeks, nasolabial folds, and chin creases.[43] This distribution was observed in the case series by Okiyama et al,[22] in which erythema was localized to the forehead, eyebrows, nasolabial folds, cheeks, and lower jaw. Allergic contact dermatitis often involves the face or eyelids, which frequently come in direct contact with the environment. Common allergens may come from cosmetics, shampoo, and fragrances, which are directly applied to the face or nearby regions.[44] For example, in the article by Suresh and Murase,[8] the first patient with dermatitis on the forearms, neck, and face patch tested positive to perfume and fragrance mix, which was a relevant allergen found in the shampoo the patient used. Similarly, the second patient patch tested positive to limonene, which was also present in the shampoo the patient used. Periocular distribution was observed in 2 patients in the case report by Yamane et al.[18] One patient had periocular and perioral distribution, which later extended to the lateral aspect of the temples and bridge of the nose. The second patient had periocular erythema with involvement of the lateral canthi and nose. The erythema was especially prominent on the medial aspect of the eyelid. Causes of periocular and perioral dermatitis include atopic dermatitis, contact dermatitis, rosacea, and periorificial dermatitis, and should be considered in patients with this distribution.[45] As demonstrated by the various cases, the distinct distribution of the facial or neck erythema may be important in differentiating the underlying cause. Because rosacealike eruptions, seborrheic dermatitis, and allergic contact dermatitis have differing approaches to treatment, distribution-based classification of facial or neck erythema may help determine the appropriate therapeutic modality for individual patients according to which underlying cause is suspected.

THE ROLE OF TOPICAL TREATMENT

Facial erythema was not reported as an adverse event in the 4 phase 3 clinical trials for dupilumab with a combined total of 2119 adult atopic dermatitis patients.[1-3] Moreover, further evaluation from a post hoc analysis of data from these phase 3 trials showed equal improvement of atopic dermatitis across different anatomic regions.[46] One potential explanation for this may be that facial or neck erythema was seen as resistant atopic dermatitis because the face and neck are common areas of atopic dermatitis involvement in adult patients. Moreover, an important difference between randomized controlled trials and reports from clinical practice is the concomitant use of topical treatment. Although topical treatments were used freely in conjunction with dupilumab in clinical practice, there were stricter guidelines in randomized controlled trials. In SOLO 1 and 2, patients underwent a 35-day washout period before beginning dupilumab, and use of any concomitant treatment was prohibited.[1] In CHRONOS, patients were permitted to use low-potency topical corticosteroid with or without topical calcineurin inhibitor on the face.[2] Similarly, CAFÉ study patients could receive low-potency topical corticosteroid on the face 14 days before starting dupilumab. If patients achieved Investigator Global Assessment (IGA) 0 by week 4, 8, or 12, they had the option of tapering to every other day. Moreover, after week 4, if patients maintained IGA 0 for 4 weeks, topical corticosteroid use could be decreased to 2 times per week but was brought back to daily application if they were not at IGA 0. Therefore, the use of topical corticosteroid was discontinued 35 days before dupilumab was begun, continued throughout the course of the study period, or tapered.[3] In contrast, patients in real-world clinical practice may have discontinued topical corticosteroid after experiencing initial improvement with dupilumab. Topical corticosteroid withdrawal is known to cause rosacealike dermatitis and may be responsible for the suspected cases of dupilumab-induced rosacea. In future studies, it may be important to pay greater attention to the use of topical corticosteroid before and during treatment to rule out topical corticosteroid-induced dermatoses, which can mimic rosacea and other mentioned etiologies.

CONCLUSION

In this systematic review, we identified 101 patients from 16 studies who were reported to have dupilumab-associated facial or neck erythema. Although 52 of 101 patients (52%) had baseline atopic dermatitis face or neck involvement, a significant portion reported different cutaneous symptoms from preexisting atopic dermatitis, suggesting a different etiology. Only 25 of 101 (25%) underwent any type of investigation. Most were treated empirically with topical medications (topical corticosteroids [43/101, 43%], topical calcineurin inhibitors [32/101, 32%], and topical antifungal agents [9/101, 9%]). Overall, improvement was observed in 29 patients, clearance in 4, no improvement in 16, and worsening in 8. Eleven patients discontinued treatment owing to this adverse event.

Various etiologies for dupilumab-associated facial or neck erythema have been proposed, including rosacea, allergic contact dermatitis, and head and neck dermatitis. These hypotheses have been based on clinical presentation, investigations, and responsiveness to treatment. In cases of suspected head and neck dermatitis, it may be useful to conduct a test for *Malassezia*-specific immunoglobulin E level or start empiric treatment with systemic antifungals.[6,16] Similarly, with suspected allergic contact dermatitis, especially in patients with a history of allergic contact dermatitis, additional patch testing after dupilumab initiation may be suggested to identify new or previously unidentified allergens to guide avoidance strategies.[8]

Limitations of this review include limited diagnostic testing, nonstandardized data collection and reporting across studies, and reliance on retrospective case reports and case series.

Dupilumab-associated facial or neck erythema should be considered in patients presenting with facial symptoms atypical of baseline disease, especially after original clearance or divergence from the improvement observed in other regions. Although larger studies with consistent investigations would help to better describe this adverse event, initial diagnostic considerations may include rosacea, allergic contact dermatitis, and head and neck dermatitis. Educating patients about this adverse event before initiation may allow prompt identification and early management, which may minimize distress or discontinuations in patients who are otherwise satisfied with their dupilumab treatment.

Conflicts of interest

Dr Piguet has received honoraria or fees for consulting or speaking for AbbVie, Almirall, Celgene, Janssen, Novartis, and Pfizer; and has received departmental support for Cardiff University from AbbVie, Almirall, Alliance, Beiersdorf UK Ltd, Biotest, Celgene, Dermal, Eli Lilly, Galderma, Genus Pharma, GlobeMicro, Janssen-Celag, LaRoche-Posay, L'Oréal, LEO Pharma, Meda, MSD, Novartis, Pfizer, Sinclair Pharma, Spirit, Stiefel, Samumed, Thornton Ross, TyPham, and UCB and for University of Toronto from Sanofi. Dr. Yeung has been a speaker, consultant, and investigator for AbbVie, Allergan, Amgen, Astellas, Boehringer Ingelheim, Celgene, Centocor, Coherus, Dermira, Eli Lilly, Forward, Galderma, GSK, Janssen, Leo, Medimmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Takeda, UCB, Valeant, and Xenon.

In the last 3 years, Dr Drucker has served as an investigator and has received research funding from Sanofi and Regeneron and has been a consultant for Sanofi, RTI Health Solutions, Eczema Society of Canada, and Canadian Agency for Drugs and Technology in Health. He has received honoraria from Prime Inc, Spire Learning, CME Outfitters, Eczema Society of Canada, and the Canadian Dermatology Association. His institution has received educational grants from Sanofi. Dr Georgakopoulos and Authors Jo and Finstad have no conflicts of interest to declare.

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