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Investigating the role of allergic contact dermatitis in residual ocular surface disease on dupilumab (ROSDD)^{☆,☆☆,☆☆☆}Jodie Raffi^{a,b,*}, Raagini Suresh^a, Harvey Fishman^c, Nina Botto^a, Jenny E. Murase^{a,d}^a Department of Dermatology, University of California, San Francisco, San Francisco, CA, United States^b Department of Dermatology, University of California, Irvine, Irvine, CA, United States^c Fishmanvision, Palo Alto, CA, United States^d Department of Dermatology, Palo Alto Foundation Medical Group, Mountain View, CA, United States

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ABSTRACT

Background: The mechanisms underlying eye-related complications with dupilumab are poorly understood.**Objective:** This study aimed to determine the incidence and characteristics of ocular complications with dupilumab and the prevalence of comorbid allergic contact dermatitis in the same subpopulation.**Methods:** This is a retrospective chart review of 48 patients with atopic dermatitis who received dupilumab. For patients with eye involvement at first follow-up, we discuss the presence of eyelid dermatitis, blepharitis, or conjunctivitis and analyze available patch test findings in patients with ocular complications while treated with dupilumab.**Results:** A total of 14 patients (29.2%) showed eye involvement while on dupilumab, all of whom experienced eye involvement prior to dupilumab. The results of the patch test were most commonly positive for emulsifier/surfactants (42.5%) and fragrances (30.4%). Nine patients experienced improvement with allergen avoidance subsequent to patch testing, and four of nine patients' conditions cleared almost entirely. This is a non-randomized study in a small cohort of patients. Only 18 patients had their disease confirmed by an ophthalmologist.**Conclusion:** All patients with eye involvement while on dupilumab had a history of eye involvement prior to dupilumab, suggest that dupilumab may encourage rather than cause ocular surface inflammation. Significant improvement after patch testing in nearly half of patients suggests that allergic contact dermatitis contributes to some cases of dupilumab-associated eye complications.© 2019 Published by Elsevier Inc. on behalf of Women's Dermatologic Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Dupilumab is a human monoclonal antibody that targets Th2 inflammation by inhibiting the IL-4 receptor alpha subunit and is approved for the treatment of moderate-to-severe atopic dermatitis (AD; [Blauvelt et al., 2017](#)). Several publications report the development or persistence of facial dermatitis, conjunctivitis, and/or

eyelid inflammation with dupilumab therapy ([Barnes et al., 2017](#); [Blauvelt et al., 2017](#); [Dalia and Marchese Johnson, 2018](#); [de Bruin-Weller et al., 2018](#); [Fukuda et al., 2019](#); [Simpson et al., 2016](#); [Treister et al., 2018](#); [Yamane et al., 2019](#)). Dupilumab, among other factors, may be directly responsible for the induction of the eye-related complications.

However, the exact pathomechanisms underlying ocular complications on dupilumab are poorly understood. A history of severe AD or conjunctivitis appears to be related to an increased risk of eye involvement while on dupilumab ([Simpson et al., 2016](#); [Wollenberg et al., 2018](#)). Based on our experience treating patients with dupilumab, we hypothesized that eye-related complications that occur with dupilumab therapy are due either to a component of undiagnosed dry-eye syndrome, allergic contact dermatitis (ACD), residual AD not fully treated with dupilumab, or a combination thereof. We sought to characterize the eye involvement in our

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★ No human subjects were included in this study. No animals were used in this study.

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patients receiving dupilumab therapy and assess the rate of ACD in these patients with ocular complications.

Methods

This study involved retrospective data collection from electronic medical records (EMRs) of patients who received 300 mg subcutaneous dupilumab for the management of AD between 2017 and 2019. Only patients with a primary dermatologic diagnosis of moderate-to-severe AD were included. The effectiveness of dupilumab and its impact on patch testing are discussed separately (Raffi et al., 2016). We use the generic umbrella term "eye involvement" to refer to any of the following three entities: eyelid dermatitis (defined as dermatitis on the upper and/or lower eyelids), blepharitis (defined as eyelid margin involvement and associated Meibomian gland dysfunction), and conjunctivitis (denoting ophthalmologist-diagnosed inflammation of the conjunctiva).

We performed a chart review of the EMRs of patients treated with dupilumab for moderate-to-severe AD during the study period. We ascertained the presence of eye involvement at two time points: prior to dupilumab therapy (at any point in EMR history) and at first follow-up on dupilumab. Of patients with eye involvement at first follow-up, we report subsequent patch test findings when available. Of note, patients with AD were selected for patch testing in accordance with the criteria determined by Chen et al. (2016). Patch test results were interpreted by the same provider in accordance with International Contact Dermatitis Research Group guidelines (Wilkinson et al., 1970).

To assess the impact of patch testing on eye involvement, we reviewed the EMRs until resolution of dermatitis was reported or until the end of the data collection period, whichever occurred first. The patch test series included the North American Contact Dermatitis Group (NACDG) standard series, Fragrances, Textile Colors & Finish, Sunscreens, and Eye Medicaments series (Chemotechnique Diagnostics, Vellinge, Sweden) and the External Agents/Emulsifiers, Corticosteroids, and Dietary Additives series (Allergeaze: SmartPractice, Calgary, Alberta, Canada). Patch tests were applied with Finn Chambers (SmartPractice, Phoenix, AZ) on Scanpor tape (Norgesplaster Alpha AS, Vennessla, Norway). The Cosmetics Tray was custom designed to include cosmetic allergens not already present in the NACDG, Fragrance, and Emulsifier Series as detailed by Suresh and Murase (2018). The study was approved by the University of California, San Francisco, institutional review board administration.

Results

Study population

A total of 48 patients with AD were receiving dupilumab at the time of data collection. The patient population consisted of adults between the ages of 17 and 92 years, with a mean age of 45 years and an equal distribution of male and female patients (n = 24 each).

Eye involvement while on dupilumab

At first follow-up, 14 patients (29.2%), including nine women (64.3%) and five men (35.7%), were found to have eye involvement, compared with 18 patients (37.5%) with a history of eye involvement prior to dupilumab therapy. Specifically, there were nine cases of allergic conjunctivitis (18.8%) while on dupilumab. Conjunctivitis, blepharitis, and eyelid dermatitis often coincided in the same patient; 8 of 14 patients (57.1%) with residual eye involvement exhibited all three types.

All 14 patients with eye involvement while on dupilumab were part of the 18-patient subcohort with longstanding eye involvement prior to dupilumab initiation. Of note, all 18 patients were experiencing some form of eye involvement, including dry eye, at the time of dupilumab initiation. Of the patients with a personal history of eye involvement, 77.8% (n = 14) were found to also have eye involvement while on dupilumab. Only 22.2% (n = 4) experienced resolution of their eye involvement while on dupilumab. There were no cases of dupilumab-associated eye involvement without a history of eye involvement. No patients stopped dupilumab due to eye-related complications.

Patch testing in patients with eye involvement

Nine of 14 patients with eye involvement while on dupilumab were patch tested without discontinuation of dupilumab. The remaining five patients were not patch tested, either due to patient preference or because the clinical features of the residual dermatitis were more indicative of AD than ACD. Patch testing involved the NACDG standard series (80 allergens), extended patch testing series, and personal products.

A total of 69 positive reactions to 40 individual allergens were detected in nine patients (Table 1). All patients had multiple positive results, including one or more positives to allergens not found on the NACDG standard 80 series (Table 2), and 52.5% (n = 21) of the positive reactions were to allergens not found on the NACDG standard series.

Allergens in the emulsifier/surfactant category accounted for the largest contributing allergen subclass (n = 17; 42.5%), representing nearly half of all reactions (n = 30; 43.5%). The next most common reactions were to fragrances (n = 21; 30.4%) and preservatives (n = 7; 10.1%). Hydroperoxides of linalool were the most commonly positive allergens (n = 6; 8.7%); next most common with four reactions each (5.8% each) were hydroperoxides of limonene and lauryl glucoside (Table 2). Patients also had relevant patch test reactions to 29 different personal products, the most common of which were shampoo/conditioner (n = 7; 24.1%) and facial moisturizer (n = 5; 18.5%; Table 3).

Four of nine patients (44.4%) displayed significant improvement in their eye complications after patch testing and were classified as having ACD-related eye involvement. One patient's condition cleared completely. Although improvements were seen in all nine patients after patch testing as measured by physician visual assessment and patient reporting, five patients continued to exhibit eye involvement beyond the extent attributable ACD alone.

Discussion

Dupilumab and eye involvement

In our cohort, dupilumab did not appear to be directly responsible for the incidence of eye involvement given that all patients reported a history of eye involvement prior to dupilumab. Prior eye involvement appears to increase the risk of eye-related complications with dupilumab. The question then seems to be, in cases such as these, whether dupilumab is inherently poor at managing AD of the eyelid region or underlying ACD is unmasked as a result of clearance of AD with dupilumab, or whether dupilumab exacerbates underlying dry-eye disease that often coexists with AD and ACD.

The role of ACD as the most frequent cause of eyelid dermatitis has been established in several studies (Amin and Belsito, 2006; Ayala et al., 2003; Cooper and Shaw, 2000; Guin, 2004; Ockenfels et al., 1997; Shah et al., 1996; Valsecchi et al., 1992) and may potentially contribute to eyelid dermatitis in patients with AD.

Table 1

Patients with eye involvement before or on dupilumab.

Patient number	Sex (M/F)	Age (years)	Time to first follow up (weeks)	History of eye involvement prior to dupilumab (Y/N)	Eye involvement on first dupilumab follow up (Y/N)	Areas of residual eye involvement at first follow up on dupilumab	Other areas of residual involvement at first follow up	Patch test performed while receiving dupilumab?	ACD vs. ROSDD	Number of positive results on patch testing
25	F	38	8	Y	Y	ED	Neck, trunk, elbows	Y	ACD	6
46	F	39	4	Y	Y	ED, B, C	Arms	Y	ACD + ROSDD	4
27	F	61	12	Y	Y	ED, B	Face, hands	Y	ACD + ROSDD	9
28	F	32	6	Y	Y	ED, B, C	Face, hand	Y	ACD + ROSDD	6
11	M	55	8	Y	Y	ED, B, C	Face	Y	ACD + ROSDD	5
14	F	57	14	Y	Y	ED, B, C	Face	Y	ACD	3
16	F	61	4	Y	Y	ED, B	Face, legs	Y	ACD	12
5	F	42	10	Y	Y	ED, B, C	Face, trunk, hands	Y	ACD + ROSDD	15
31	M	53	8	Y	Y	ED	Scalp, face, trunk	Y	ACD	8
44	M	52	8	Y	Y	B, C	Legs	N	n/a	n/a
24	M	47	8	Y	Y	ED, B, C	Face, trunk	N	n/a	n/a
26	M	48	16	Y	Y	ED	Face	N	n/a	n/a
2	F	76	8	Y	Y	ED, B, C	Neck, hands	N	n/a	n/a
39	F	29	4	Y	Y	ED, B, C	Face, trunk, arms, hands	N	n/a	n/a
29	F	28	8	Y	N	None	Hands, legs	n/a	n/a	n/a
18	F	56	8	Y	N	None	Face	n/a	n/a	n/a
15	F	56	8	Y	N	None	Face, neck, arms	n/a	n/a	n/a
13	M	45	8	Y	N	None	Face, trunk, arms	n/a	n/a	n/a

ACD, allergic contact dermatitis; B, blepharitis; C = conjunctivitis; ED, eyelid dermatitis; F, female; M, male; N, no; n/a, not available; ROSDD, residual ocular dermatitis on dupilumab; Y, yes.

Although the data are mixed with regard to the incidence of ACD in patients with AD, several factors may contribute to an increased risk of ACD (Chen et al., 2016), including increased vulnerability of an inflamed barrier to sensitization (Huang et al., 2011; Jakasa et al., 2007; Takahashi et al., 2011; Thyssen et al., 2014), increased risk of irritant contact dermatitis in AD (Nassif et al., 1994), and chronic exposure to sensitizing agents in topical emollients (Hamann et al., 2015; Mailhol et al., 2009).

Given the spectrum of eye and/or eyelid complications observed with dupilumab, the term “dupilumab-induced ocular surface disease” has been proposed (Zirwas et al., 2018). This term implies that dupilumab is the cause of ocular surface disease. However, we hypothesize that at least a portion of ocular complications while on dupilumab are due to previously undiagnosed dry eye disease, ACD, or an intrinsic inability of dupilumab to appropriately treat dermatitis of the eye and eyelid region rather than ocular involvement arising de novo from the influence of dupilumab. In fact, an inverse relationship between conjunctivitis and serum dupilumab concentration has been observed, indicating that local undertreatment may be occurring (Simpson and Akinlade, 2017). Therefore, we refer to residual ocular surface disease not clearing with dupilumab therapy or patch testing as residual ocular surface disease on dupilumab (ROSDD).

ROSDD in particular refers to ocular complications while on dupilumab in which ACD has been excluded as the cause. We believe that ROSDD represents an exacerbation of a baseline elevated susceptibility in certain individuals, demonstrated by a history of dry eye, eyelid dermatitis, blepharitis, or conjunctivitis. In our experience, patients with AD limited to other areas of the body—and no history of dry eye or other ocular complications—do not go on to develop eye-related complications while on dupilumab. Among patients with a personal history of eye-related AD, those with active eye disease (including mild cases of dry eye) at the time of dupilumab initiation appear to be particularly at risk for exacerbation of eye complications during the course of dupilumab therapy. Indeed, of the 18 patients in this cohort with preex-

isting eye involvement, 77.8% went on to experience eye involvement while on dupilumab, but 22.2% experienced clearance of ocular involvement with dupilumab therapy.

Patch testing in nine patients with residual eye involvement while on dupilumab resulted in various levels of clinical improvement in all patients. Importantly, four patients exhibited a significant improvement of eyelid dermatitis and a reduction in pruritus after patch testing, requiring only sporadic use of topical corticosteroids. One patient's condition cleared completely by 8-week follow-up. In these four cases, eye involvement was attributed entirely to ACD.

However, even with patch testing and allergen avoidance, five patients experienced continued ocular involvement and were diagnosed with ROSDD. ROSDD was not observed in any patient without a history of eye involvement prior to the use of dupilumab. The consistent, longstanding history of AD-related eye complications prior to the initiation of dupilumab in each patient with ROSDD suggests that eye involvement while on dupilumab, at least in a subset of patients, may be a result of incompletely controlled AD rather than an adverse effect caused by dupilumab. Notably, all ROSDD patients experienced improvement, albeit incomplete, with patch testing. Patients with longstanding dry eye while on dupilumab can benefit from non-steroid topical ophthalmological therapy that includes anti-inflammatory and antihistamine ophthalmic drops (Shen et al., 2018).

The preponderance of eye complications in patients with prior ocular disturbance suggests that the eye may be uniquely susceptible to influence by dupilumab. There have been multiple cases of new-onset conjunctivitis or eyelid inflammation in patients receiving dupilumab or with a strong temporal relationship to dupilumab administration (Bakker et al., 2019; Dalia and Marchese Johnson, 2018; Fukuda et al., 2019; Shen et al., 2018; Wollenberg et al., 2018; Zirwas et al., 2018). In one study, only 64% of patients receiving dupilumab for AD had documented ocular surface disturbance prior to medication initiation, but only 30% had been seen by an ophthalmologist at baseline (Maudinet et al., 2019). Some

Table 2
Allergens positive on patch testing.

Allergen subclass	n (% positive reactions)	On NACDG Core 80 in Jan 2019? (Y = yes, N = no)
<i>Emulsifiers and surfactants</i>		
Propylene glycol 30% pet	1 (1.4%)	Y
Cocamidopropylbetaine 1% aq	1 (1.4%)	Y
Oleamidylpropyl dimethylamine 0.1% aq	2 (2.9%)	Y
Coconut diethanolamide 0.5% pet	1 (1.4%)	Y
Decyl glucoside 3% pet	3 (4.3%)	Y
Amerchol L101 50% pet	3 (4.3%)	Y
Lanolin alcohol, 30% pet	3 (4.3%)	N
Wool alcohols ointment 100%	3 (4.3%)	N
Lauryl glucoside 3% pet	4 (5.8%)	N
Stearyl alcohol 30% pet	2 (2.9%)	N
Cetylstearylalcohol 20% pet	1 (1.4%)	N
Butylhydroxyanisole 2% eth	1 (1.4%)	N
Butylhydroxytoluene 2% pet	1 (1.4%)	N
Octyl gallate 0.25% pet	1 (1.4%)	N
Tween 40, 10% pet	1 (1.4%)	N
Tween 80, 10% pet	1 (1.4%)	N
Dodecyl gallate 0.3% pet	1 (1.4%)	N
Total (17 allergens)	30 (43.5%)	6 Y (35.2%), 11 N (64.7%)
<i>Fragrances</i>		
Hydroperoxides of linalool 1% pet	6 (8.7%)	Y
Hydroperoxides of limonene 0.3% pet	4 (5.8%)	Y
Fragrance mix 2 14% pet	2 (3.3%)	Y
Balsam of peru 25% pet	1 (1.4%)	Y
Perfume mix 6.0 pet	3 (4.3%)	N
Cinnamic alcohol 2.0 pet	2 (2.9%)	N
Amyl cinnamyl alcohol 5.0 pet	1 (1.4%)	N
D-Limonene 10.0 pet	1 (1.4%)	N
Narcissus absolute 2.0 pet	1 (1.4%)	N
Total (9 allergens)	21 (30.4%)	4 Y (44.4%), 5 N (55.6%)
<i>Preservatives</i>		
Iodopropynyl butyl carbamate 0.2% pet	2 (2.9%)	Y
Benzyl alcohol 10.0 soft	1 (1.4%)	Y
Benzalkonium chloride 0.1% aq	2 (2.9%)	N
Phenyl salicylate (salol) 1% pet	1 (1.4%)	N
Sodium benzoate 5% pet	1 (1.4%)	N
Total (5 allergens)	7 (10.1%)	2 Y (40%), 3 N (60%)
<i>Topical corticosteroid and antibiotic agents</i>		
Budesonide 0.1% petrolatum	3 (4.3%)	Y
Neomycin sulphate 20% pet	1 (1.4%)	Y
Benzoyl peroxide 1% pet	1 (1.4%)	Y
Aclometasone 17-21-dipropionate 1% pet	2 (2.9%)	N
Total (4 allergens)	7 (10.1%)	3 Y (75%), 1 N (25%)
<i>Metals</i>		
Potassium dichromate 0.25% pet	1 (1.4%)	Y
Nickel sulfate hexahydrate 1.0 pet	1 (1.4%)	Y
Cobalt (II) chloride hexahydrate 1.0 pet	1 (1.4%)	Y
Total (3 allergens)	3 (4.3%)	3 Y (100%)
<i>Hairdressing</i>		
Ammonium persulfate	1 (1.4%)	N
Total (1 allergen)	1 (1.4%)	1 N (100%)

NACDG, North American Contact Dermatitis Group.

Table 3
Personal products positive on patch testing.

Product name (n = 29)
Apothecare Essentials Shampoo 10%
Shea moisturizer daily hydration shampoo 10%
Under the Canopy citrus & lime conditioning shampoo 10%
Nexxus Therappe Shampoo
Free and clear shampoo
Aveda shampoo
Aveda conditioner
Pharmacy green clean balm
Shea butter
Laneige Skin Emulsion
Laneige Moisture Essence
Laneige moisture cream
Unidentified facial moisturizer
Cetaphil gentle cleanser
Neutrogena hydroboost water hyaluronic acid
Free and Clear liquid cleanser
CeraVe sunscreen
La Roche-Posay Anthelios 50 mineral sunscreen
Clinique eye serum
Pataday ophthalmologic solution
Delicate wash (eye)
Ultra clarity lens
Trader Joe's coconut oil
Olive oil soap
Frankincense oil
California body wash oil
Robathol bath oil
Tarte eyeliner
Gillette shave foam

authors suggest that dupilumab-associated conjunctivitis is of an etiology not classically associated with AD or is a new entity altogether, explained by the close temporal relationship to dupilumab administration, unique clinical ophthalmologic findings (Shen et al., 2018), or unique histological findings (Bakker et al., 2019). Additionally, ocular complications were not observed in dupilumab trials of patients with asthma or nasal polyposis (Simpson et al., 2016), suggesting a unique interplay between AD and dupilumab resulting in ocular disturbance.

Of note, allergic conjunctivitis also appears to be associated with dupilumab, as seen in all nine of our cases and in a phase III clinical trial (de Bruin-Weller et al., 2018). The occurrence of allergic eye disease with dupilumab is supported by the increase in eosinophils in patients with ocular complications while on dupilumab (Thyssen et al., 2017). We have observed comorbid AD and ACD affecting the eye and eyelid region, but whether the remaining cases of ROSDD are due to recalcitrant AD or a form of dupilumab-induced eye and eyelid inflammation requires more study. To our knowledge, our study is the first to date to address the possibility that undiagnosed ACD and/or dry eye disease is a factor in persistent eye involvement while on dupilumab.

Patch testing: eye involvement while on dupilumab

All nine patients who were patch tested had multiple positive results, indicating comorbid ACD. Hydroperoxides of linalool were the most common positive allergen (8.7%; n = 6), with hydroperoxides of limonene among the next most common (5.8%; n = 4). The high rate of fragrance allergy in this cohort (30.4%) echoes the results from multiple other studies that found fragrances to be major agents in eyelid ACD (Amin and Belsito, 2006; Ayala et al., 2003; Ockenfels et al., 1997; Shah et al., 1996; Valsecchi et al., 1992). High rates of contact sensitization to hydroperoxides of linalool and limonene reflect the high prevalence in the literature (Assier, 2018; Dittmar and Schuttelaar, 2019; Nath et al., 2017)

and reinforce these as high-risk allergens. Although evidence exists that linalool and limonene may frequently cause irritant reactions (Assier, 2018), we found four of six reactions to be more pronounced at 5 days than at 2 days, which supports a diagnosis of ACD. The other two reactions experienced a stable or decrease response. Hydroperoxides of linalool and limonene are found on the Chemotechnique North American 80 Comprehensive Series but not the SmartPractice North American Series or T.R.U.E test.

Emulsifiers and surfactants accounted for the largest number of reactions in this group (43.5%), which is higher than noted in other studies (Corazza et al., 2016). This may be due to the nearly ubiquitous presence of emulsifiers and surfactants in topical preparations and personal products, to which a population with moderate-to-severe AD would be predisposed to prolonged exposure.

Among the emulsifiers/surfactants, there were seven reactions to alkyl glucoside surfactants, including decyl glucoside (n = 3) and lauryl glucoside (n = 4). All three individuals with decyl glucoside allergy had a concurrent lauryl glucoside allergy. Alkyl glucosides are used in both leave-in and rinse-off products for surfactant properties and occasionally as emulsion stabilizers in sunscreen and cleansing products (Loranger et al., 2017). Decyl glucoside is the most commonly used alkyl glucoside surfactant (Milam and Cohen, 2019) with increased rates of sensitization observed in the 2015–2016 NACDG testing period (DeKoven et al., 2018; Milam and Cohen, 2019). Lauryl glucoside has the highest concentration in leave-in products (8%; Loranger et al., 2017). One patient in this cohort had ACD rather than ROSDD, and the condition cleared significantly after discontinuing a shampoo with decyl glucoside.

Amerchol L101 (lanolin alcohol) and wool alcohol ointment are derivatives of lanolin, used in skin creams and ointments to soothe irritated skin or facilitate cutaneous absorption of topical products (Warshaw et al., 2009). Amerchol L101 has been found in prior studies to detect lanolin allergy more readily than wool alcohols (Corazza et al., 2016; Matthieu and Docks, 1997) and medical grade lanolin (DeKoven et al., 2018), and is currently among the top 15 most frequently positive-testing allergens (DeKoven et al., 2018). In our study, there were three reactions each to Amerchol L101, wool alcohols, and lanolin alcohol (4.3% each). Two patients reacted to all three lanolin derivatives.

Budesonide, a corticosteroid, was also a commonly positive-testing allergen (n = 3). ACD to topical corticosteroids represents a small but important share of contact dermatitis cases—expected, as desonide is the most commonly used corticosteroid for eyelid inflammation. The risk of sensitization to corticosteroids increases with a greater length of exposure and a history of AD, hand dermatitis, and stasis dermatitis (Hengge et al., 2006). In 10-year retrospective patch testing data from the NACDG, budesonide was the second most common positive-testing corticosteroid allergen after tixocortol pivalate (Pratt et al., 2018).

Relevant positive reactions were also seen to a number of personal products, most commonly shampoo/conditioner (n = 7) and facial moisturizers (n = 5), as well as facial cleansers, eye medications, detergents, and sunscreens (Table 3). Eyelid ACD to shampoo can be difficult to differentiate from irritant contact dermatitis because these conditions often have a similar presentation. However, there is value in patch testing to shampoo if this is a suspected source of ACD. Factors strongly suggestive of eyelid ACD to shampoo include cases in which an increased strength of positive reaction is seen on a second instance of patch testing and cases in which improvement is seen with prudent avoidance of the shampoo.

A substantial portion (52.5%) of positive reactions were to allergens not found on the NACDG standard series, including the fragrance, preservatives, emulsifiers and surfactants, corticosteroids,

metals, and hairdressing series. Standard patch-test series, such as the NACDG and T.R.U.E. test, are commonly used by dermatologists for practical purposes; however, using only these standard series leaves out many key allergens and can lead a provider to mistakenly rule out a diagnosis of ACD. The high rate of relevant positive results to non-standard series allergens highlights the necessity of patch testing, both to extended series and personal products, to properly diagnose ACD.

This study has several limitations, notably its small sample size. Only the 18 patients in the eye cohort had their disease confirmed by an ophthalmologist; therefore, specific ophthalmologic findings may have been overlooked. This study is a retrospective chart analysis and could not be randomized to reduce the influence of confounders or standardize patch-testing series and protocols.

Conclusion

Eye involvement, including eyelid dermatitis, blepharitis, and conjunctivitis, was fairly common within our cohort, occurring in nearly 30% of patients who received dupilumab. All patients with eye involvement while on dupilumab had a longstanding history of eye involvement prior to the initiation of dupilumab, suggesting that dupilumab may exacerbate existing dry eye disease via eyelid and/or conjunctival inflammation rather than being an organic cause of complications in these cases.

Among the patients who were patch tested, there were multiple positive results per patient, most commonly in the emulsifier/surfactant and fragrance categories. Significant improvements in eye involvement after patch testing occurred in nearly half of patients, indicating the contribution of ACD to some cases of dupilumab-associated eye complications. In the remaining patients, an incomplete improvement was seen after patch testing, which suggests that dupilumab may not completely treat AD of the eye and eyelid region.

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