Characterization of Residual Facial Dermatitis during Dupilumab Therapy: A Retrospective Chart Review to Delineate the Potential Role of Expanded Series Patch Testing

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Background: **The underlying mechanisms of residual facial dermatitis on dupilumab (RFDD) in patients dupilumab therapy for atopic dermatitis are poorly understood.**

Objective: **We sought to determine the incidence of RFDD in patients receiving dupilumab and the rate of resolution of RFDD after expanded series patch testing (ESPT) and allergen avoidance.**

Methods: **This is a retrospective chart review of 80 patients with atopic dermatitis who were evaluated for RFDD after treatment with dupilumab. Expanded series patch testing findings and response to allergen avoidance were assessed in the subset of patients with RFDD who subsequently underwent ESPT while continuing to receive dupilumab.**

Results: **Forty-nine patients (61.3%) experienced facial dermatitis before initiating dupilumab. Thirty-five patients (43.8%) experienced RFDD after starting dupilumab. Of the 14 patients with RFDD who received ESPT, 92.9% had 1 or more relevant positive patch test results, with 50% of such patients being mostly to completely clear of facial dermatitis after allergen avoidance. Importantly, 50.6% of the positive reactions to allergens were not included on the North American Contact Dermatitis Group Core 80.**

Conclusions: **Many patients with RFDD benefit from patch testing and subsequent allergen avoidance. Expanded series patch testing should be offered to patients who experience RFDD after beginning dupilumab therapy to ensure that such patients have eliminated any exogenous component of their dermatitis, such as concomitant allergic contact dermatitis.**

Dupilumab, an anti-interleukin (IL)-4 receptor α human monoclonal antibody that inhibits T helper 2 pathway IL-4 and IL-13 signaling, is effective in treating moderate-to-severe atopic dermatitis (AD).[1] New-onset and recalcitrant facial dermatitis (FD) has been reported in patients receiving dupilumab therapy.[2–11] Although hypotheses regarding the etiology of paradoxical facial flaring on dupilumab include site-specific treatment failure,[9] hypersensitivity reaction to dupilumab,[9] hypersensitivity to facial *Malassezia* species,[4,7] new-onset rosacea,[5] and flaring of allergic contact dermatitis (ACD),[3,8] the underlying mechanisms responsible for residual FD on dupilumab (RFDD) in patients during dupilumab therapy are poorly understood.[12]

Given the reports of patients experiencing significant improvement in RFDD[8] and ocular surface disease[13] after patch testing, we hypothesized that comprehensive patch testing of patients with RFDD using expanded series patch testing (ESPT) and subsequent allergen avoidance would increase the rate of FD resolution in such patients. Our study aimed to characterize the incidence of RFDD in patients receiving dupilumab for classic AD and determine the rate of resolution in patients who underwent patch testing and allergen avoidance.

METHODS

Study Population

This study involved retrospective data collection from medical records of patients who received 300-mg dupilumab every other week for the management of AD between May 2017 and July 2020. Only patients with a primary diagnosis of AD were included in the study. Demographics and relevant medical history, such as age, sex, history of childhood atopy, comorbid dermatologic disease, and treatment

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history of AD, were recorded. The study was approved by the institutional review board of the University of California, San Francisco.

Response to Dupilumab in Our Cohort

Reduction of clinical severity during treatment with dupilumab was determined by asking patients to report the percent improvement in their AD compared with baseline at the patient's first follow-up visit. Sites of residual dermatitis as well as any dupilumab-associated adverse effects were documented.

Patch Testing While Receiving Dupilumab Treatment

To evaluate the impact of patch testing on RFDD, patients with RFDD and morphology suspicious for a potential ACD component were patch tested while continuing dupilumab, as described by Raffi et al[13] and Suresh and Murase.[8] Of note, patients were patch tested with the North American Contact Dermatitis Group (NACDG) standard series and expanded series, including the fragrances, textile colors & finish, sunscreens, and eye medicaments (Chemotechnique Diagnostics, Vellinge, Sweden) and the external agents/emulsifiers, corticosteroids, and dietary additives (allergEAZE; SmartPractice, Calgary, Alberta, Canada). In addition, some patients were tested with a cosmetics tray that was custom designed to include cosmetic allergens not already present in the NACDG, fragrance, and emulsifier series, as previously published.[8]

Facial Dermatitis After Patch Testing and Allergen Avoidance

Patients were asked in the office visit months after their patch test to evaluate the utility of the patch testing specifically in how skin care product change and allergen avoidance improved their dermatitis. Patients were asked to rate the utility of patch testing in improving their RFDD as either "not," "somewhat," "mostly," or "completely" helpful based on their experience with a trial of allergen avoidance after patch testing. Use and frequency of use, if applicable, of topical medications on the face were recorded.

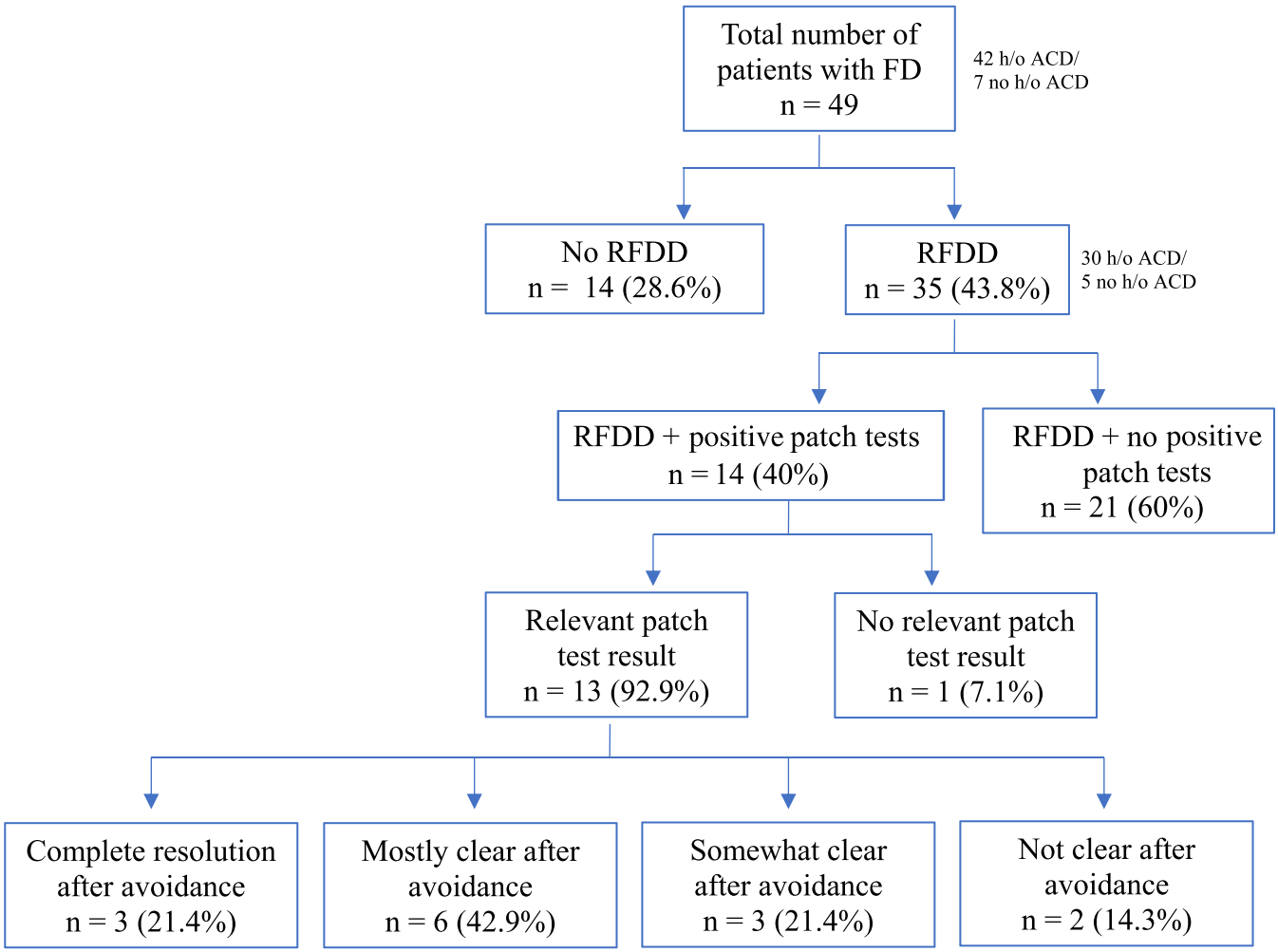

Figure 1. Schematic of the patient cohort and outcomes after ESPT. FD, facial dermatitis, RFDD, residual facial dermatitis on dupilumab.

TABLE 1. Patients With FD Before or on Dupilumab

Patient Number	Sex, M/F	Age, y	AD vs AD + ACD	Time to First f/u After Starting Dupilumab, wk	FD at First f/u (No, Mild, Mod, Severe)	% of AD Clear at First f/u	Time to Most Recent f/u After Starting Dupilumab, wk	FD at Most Recent f/u (No, Mild, Mod, Severe)	Active Use of Topicals for Face and Frequency	Patch Test Performed Before Dupilumab? (Y/N)	Patch Test Performed While Receiving Dupilumab? (Y/N)	No. Positive Results on Patch Testing	Patient Assessment of Patch Test Utility in Improving FD
Group 1: dupilumab FD + patch testing													
3	F	34	AD + ACD	7	Mod	80%	32	Mild	Dn bid, Tc prn	Y	Y	15	Mostly (90%)
5	F	59	AD + ACD	14	Mild	95%	52	Mod	Dn bid	Y	Y	20	Somewhat (40%)
7	M	47	AD + ACD	8	Mild	85%	52	No	Tc qwk	Y	Y	1	Not
9	M	57	AD + ACD	12	Mod	75%	30	Mod	Dx prn	Y	Y	13	Somewhat (30%)
17	F	63	AD + ACD	3	Mild	90%	100	No	none	Y	Y	17	Completely (100%)
20	F	44	AD + ACD	10	Mod	25%	88	Mild	Tc bid	Y	Y	20	Mostly (90%)
24	F	41	AD + ACD	4	Mod	50%	88	Mild	Cl biw	N	Y	7	Mostly (99%)
28	F	58	AD + ACD	9	Mild	99%	108	Mod	Dx bid	Y	Y	0	Not
29	F	52	AD + ACD	9	Mod	70%	52	Mild	Dx bid	Y	Y	8	Somewhat (30%)
36	M	39	AD + ACD	8	Mod	90%	104	Mild	Tc bid	Y	Y	12	Mostly (90%)
47	F	39	AD + ACD	11	Mild	65%	44	Mild	Tr prn	N	Y	7	Mostly (85%)
52	F	34	AD + ACD	24	Mod	95%	140	No	None	N	Y	4	Somewhat (45%)
59	M	34	AD + ACD	8	Mild	90%	96	Mild	None	N	Y	5	Mostly (90%)
63	F	57	AD + ACD	8	Mild	90%	104	Mild	Dx bid	Y	Y	5	Mostly (75%)
Group 2: dupilumab FD + no patch testing													
1	F	44	AD + ACD	132	Mild	*NA	132	Mild	None	N	N	NA	N/A
64	M	62	AD	16	Mild	80%	40	Mild	Tc bid	N	N	NA	NA
8	M	49	AD + ACD	9	Mild	80%	104	Mild	Tc prn	Y	N	NA	NA
15	M	56	AD + ACD	14	Mod	50%	56	Mild	Tc bid	Y	N	NA	NA
23	F	60	AD + ACD	12	Mod	20%	12	Mod	Tc prn	Y	N	NA	NA
70	F	31	AD	4	Mod	95%	140	Mild	None	N	N	NA	NA
30	F	20	AD + ACD	4	Mild	80%	104	Mild	Tc prn	Y	N	NA	NA
34	F	59	AD + ACD	12	Mild	90%	12	Mild	Dn prn	Y	N	NA	NA
44	F	47	AD + ACD	4	Mild	80%	4	Mild	None	Y	N	NA	NA
45	M	51	AD + ACD	13	Mod	30%	72	No	None	Y	N	NA	NA
50	M	37	AD	12	Mod	75%	12	Mod	Tc bid prn	Y	N	NA	NA
76	M	59	AD + ACD	28	Mild	50%	64	Mild	None	N	N	NA	NA
77	M	50	AD + ACD	16	Mild	90%	31	Mild	Tc bid	N	N	NA	NA
62	F	42	AD + ACD	6	Mild	20%	20	Mild	None	Y	N	NA	NA
80	F	40	AD	8	Mild	90%	92	Mild	Tc prn	N	N	NA	NA
Group 3: dupilumab FD that improved with dupilumab alone													
10	M	69	AD + ACD	8	No	95%	32	No	None	Y	NA	NA	NA
68	M	32	AD	8	Mild	85%	32	No	Tc prn	N	NA	NA	NA
12	M	60	AD + ACD	23	No	95%	116	No	None	Y	NA	NA	NA
13	F	30	AD + ACD	16	No	90%	16	No	None	Y	NA	NA	NA
16	F	68	AD + ACD	3	Mild	80%	68	No	None	Y	NA	NA	NA
21	F	52	AD + ACD	3	No	90%	130	No	Tc prn	Y	NA	NA	NA
71	F	29	AD	34	No	100%	40	Mild	None	N	NA	NA	NA
27	M	66	AD + ACD	8	Mod	90%	32	No	Tc bid	Y	NA	NA	NA
32	F	39	AD + ACD	4	Mod	60%	80	No	None	Y	NA	NA	NA
37	F	58	AD + ACD	9	No	100%	9	No	None	Y	NA	NA	NA

TABLE 1. *(Continued)*

Patient Number	Sex, M/F	Age, y	AD vs AD + ACD	Time to First f/u After Starting Dupilumab, wk	FD at First f/u (No, Mild, Mod, Severe)	% of AD Clear at First f/u	Time to Most Recent f/u After Starting Dupilumab, wk	FD at Most Recent f/u (No, Mild, Mod, Severe)	Active Use of Topicals for Face and Frequency	Patch Test Performed Before Dupilumab? (Y/N)	Patch Test Performed While Receiving Dupilumab? (Y/N)	No. Positive Results on Patch Testing	Patient Assessment of Patch Test Utility in Improving FD
38	M	52	AD + ACD	20	No	100%	28	No	Tc qad	Y	NA	NA	NA
40	F	63	AD + ACD	10	Mild	90%	80	No	Dn prn	Y	NA	NA	NA
39	F	74	AD + ACD	10	No	99%	12	No	None	Y	NA	NA	NA
73	M	60	AD	36	No	100%	84	No	None	N	NA	NA	NA
41	F	60	AD + ACD	5	No	75%	24	Mild	Tc bid	Y	NA	NA	NA
42	F	72	AD + ACD	2	Mild	100%	12	No	None	Y	NA	NA	NA
43	M	55	AD + ACD	1	No	95%	132	Mild	None	Y	NA	NA	NA
51	M	55	AD + ACD	9	No	60%	52	Mild	Dx prn	Y	NA	NA	NA
54	F	79	AD + ACD	4	No	99%	52	Mild	Hc prn	Y	NA	NA	NA
55	F	78	AD + ACD	8	No	85%	88	No	None	Y	NA	NA	NA

**NA, started dupilumab for allergic rhinitis purposes, data unavailable.*

ACD, allergic contact dermatitis; AD, atopic dermatitis; bid, twice a day; biw, biweekly; Cl, clocortolone; Dn, desonide; Dx, desoximetasone; F, female; f/u, follow-up; Hc, hydrocortisone; M, male; mod, moderate; N, no; NA, not available; prn, as needed; qad, every other day; qwk, every week; Tl, tacrolimus; Tr, triamcinolone; Y, yes.

RESULTS

Study Population

A total of 80 patients with a primary diagnosis of AD receiving dupilumab were included. The study population included 47 female (58.8%) and 33 male (41.3%) patients, ages 19–93 years, with a mean age of 55 years.

Before receiving dupilumab, 37.5% of the patients had a history of asthma, 61.3% had a history of childhood eczema, and 58.8% had a history of environmental allergens. In addition, before starting dupilumab, 75.0% of the patients had a comorbid diagnosis of ACD, 8.8% had primary hand dermatitis, 11.3% had lichen simplex chronicus/prurigo nodularis, 6.3% had nummular dermatitis, 25.0% had conjunctivitis, blepharitis, or dry eyes, and 61.3% had facial involvement of AD. Of note, 69.1% of the patients had received patch testing before initiating dupilumab.

Before starting dupilumab, 65.0% patients had received systemic glucocorticoids. In addition, 26.3% patients had received azathioprine, cyclosporine, methotrexate, or mycophenolate mofetil before beginning dupilumab. All patients had discontinued any other systemic treatments before initiating dupilumab therapy.

Facial Dermatitis Before Dupilumab Therapy

Forty-nine patients (61.3%) experienced FD before initiating dupilumab (Fig. 1), 30 of whom were female (61.2%) and 19 of whom were male (38.8%; Table 1). Forty-two patients (85.7%) with FD had comorbid ACD.

Response to Dupilumab

At the first follow-up appointment, which occurred in an average of 11.7 weeks after starting dupilumab, the average improvement from baseline was 78.3% among all 80 patients. Comparably, the 49 patients with FD before initiating dupilumab averaged 79.1% improvement at the first follow-up. No patients discontinued dupilumab therapy.

Adverse Effects While Receiving Dupilumab Treatment

Fifteen patients (18.8%) experienced 1 or more adverse effects while on dupilumab, 11 of whom reported ocular symptoms, such as dryness or conjunctivitis. Two patients reported dry skin, 2 reported mild injection site reactions, 1 reported joint pain, 1 reported red sweat 3–4 days after injections, and 1 reported localized itching to the left abdomen and chest in the absence of any lesions. No patients discontinued dupilumab therapy because of adverse effects.

Dupilumab FD After Starting Dupilumab

Thirty-five patients (43.8%) experienced RFDD after starting dupilumab, including 22 women (62.9%) and 13 men (37.1%), whereas 14 of the 49 patients (28.6%) who had experienced FD before dupilumab experienced FD resolution by the first follow-up on dupilumab alone. Thirty of the patients (85.7%) with RFDD had a history of ACD. Of the

TABLE 2. Allergens Positive on Patch Testing While Receiving Dupilumab Treatment

Allergen	No. Positive Reactions	On NACDG Core 80 (2018 Edition)? (Y/N)
Emulsifiers/surfactants (n = 15)		
Amerchol L-101 50% pet	3 (3.7%)	Y
Butylhydroxyanisole 2% eth	1 (1.2%)	N
Butylhydroxytoluene 2% pet	1 (1.2%)	N
Cocamidopropyl betaine 1.0% aq	2 (2.5%)	Y
Decyl glucoside 5% pet	4 (4.9%)	Y
Lanolin alcohol 30% pet	3 (3.7%)	N
Lauryl glucoside 3.0 pet	3 (3.7%)	N
Octyl gallate 0.25% pet	1 (1.2%)	N
Oleamidyl propyl dimethylamine 0.1% aq	2 (2.5%)	Y
Propylene glycol 100% aq	1 (1.2%)	N
Propylene glycol 30% pet	1 (1.2%)	Y
Stearyl alcohol 30% pet	2 (2.5%)	N
Tween 40 10% pet	1 (1.2%)	N
Tween 80 10% pet	1 (1.2%)	N
Wool alcohols ointment 100%	3 (3.7%)	N
Fragrances (n = 12)		
Amyl cinnamyl alcohol 5.0% pet	1 (1.2%)	N
Citral 2.0% pet	1 (1.2%)	N
D-Limonene 10.0% pet	1 (1.2%)	N
Eugenol 2.0% pet	1 (1.2%)	N
Fragrance mix II 14% pet	4 (4.9%)	Y
Hydroperoxides of limonene 0.3% pet	5 (6.2%)	Y
Hydroperoxides of linalool 1.0% pet	8 (9.9%)	Y
Linalool synthetic 10.0% pet	1 (1.2%)	N
Lyral 5% pet	3 (3.7%)	N
Myroxylone pereirae resin (balsam of Peru) 25% pet	1 (1.2%)	Y
Narcissus absolute 2.0% pet	1 (1.2%)	N
Perfume mix 6.0% pet	3 (3.7%)	N
Hairdressing (n = 1)		
Ammonium persulfate 2.5% pet	2 (2.5%)	N
Metals (n = 2)		
Nickle sulfate hexahydrate 5.0% pet	1 (1.2%)	Y
Potassium dichromate 0.25% pet	2 (2.5%)	Y
Preservatives (n = 7)		
Benzalkonium chloride 0.1% aq	4 (4.9%)	N
Benzyl alcohol 10.0% sof	1 (1.2%)	Y
Iodopropynyl butyl carbamate 0.2% pet	1 (1.2%)	Y
Phenyl salicylate (salol) 1% pet	1 (1.2%)	N
Quaternium-15 2.0% pet	1 (1.2%)	Y
Sodium benzoate 5% pet	1 (1.2%)	N
Thimerosal 0.1% pet	1 (1.2%)	Y
Topical corticosteroid and antibiotic agents (n = 4)		
Alclometasone-17,21-dipropionate 1.0% pet	2 (2.5%)	N
Budesonide 0.01% pet	2 (2.5%)	Y
Kanamycin sulfate 10% pet	1 (1.2%)	Y
Neomycin sulfate 20% pet	2 (2.5%)	N

aq, aqueous; eth, ethanol; N, no; pet, petrolatum; sof, softisan; Y, yes.

patients with RFDD, 21 (60%) had mild FD and 14 (40%) had moderate FD at their first follow-up appointment. No patients experienced new-onset FD after initiating dupilumab in our study.

Patch Testing While Receiving Dupilumab Treatment

Fourteen of 35 patients (40%) with RFDD received patch testing while receiving dupilumab treatment. (Table 1, group 1), given that

TABLE 3. Personal Products Positive on Patch Testing

Product Name (n = 43)
All detergents
Apothecare essentials shampoo
Aveda conditioner
Aveda shampoo
CeraVe daily moisturizing lotion
CeraVe skin renewing night cream
CeraVe sunscreen
Cetaphil body wash
Cetaphil Pro eczema soothing moisturizer
Clinique eye serum
Delicate wash
FragFre organics aloe vera gel face & body
Free & Clear liquid cleanser
Free & Clear shampoo
Gillette shave foam
Hand soap
Kirkland dish soap
Korres sunscreen C
La Roche-Posay 50+ lotion
La Roche-Posay Anthelios 50 mineral sunscreen
Laneige moisture cream
Laneige moisture essence
Laneige skin emulsion
Lily of the desert aloe vera gel
Neutrogena gel cream
Neutrogena hydrating serum
Nexxus Therappe shampoo
Old Spice sport deodorant
Olive oil soap
Pataday ophthalmologic solution
Pazeo
Pharmacy green clean balm
Robathol bath oil
Shea butter
Shea moisturizer daily hydration shampoo
Shishiedo cream
Tarte eyeliner
Thieves toothpaste
Tide detergent
Tide Free & Clear
Trader Joe's coconut oil
Under the canopy citrus and lime conditioning shampoo
Unbranded face cream

TABLE 4. Extended Series Patch Test Results in Patients With Dupilumab FD Before and After Dupilumab

	Patch Test 1 (Months Before [–] Starting Dupilumab)	Series Tested	PT 1 Positives	PT 2 Date (Months Before [–] or After [+] Starting Dupilumab)	Series Tested	PT 2 Positives	PT 3 Date (Months Before [–] or After [+] Starting Dupilumab)	Series Tested	PT 3 Positives	PT 4 Date (Months Before [–] or After [+] Starting Dupilumab)	Series Tested	PT 4 Positives
Patients 3	– 3	NACDG, emulsifiers, corticosteroids	None	+ 11	Cosmetics, fragrances	Cosmetics: butylhydroxyanisole 2% eth, butylhydroxytoluene 2% pet, sodium benzoate 5% pet Fragrance: D-limonene 10.0 pet, hydroperoxide of linalool 1% pet, hydroperoxide of limonene 0.3% pet						
5	– 17	NACDG, sunscreen, emulsifiers	NACDG: fragrance mix II 14% pet, *Myroxylon pereirae* resin (balsam of Peru) 25% pet, fragrance mix I 8% pet, glutaraldehyde 1% pet Emulsifier: NA 89NA Amerchol l101 50% pet	+ 7	Corticosteroids, cosmetics, dietary, eye, fragrance	Eye: benzalkonium 0.1% pet Fragrance: linalool synthetic 10.0 pet, 1+/1+ hydroperoxide of linalool 1.0% pet, hydroperoxide of limonene 0.3% pet						
7	– 48	NACDG	NACDG: fragrance mix II, Quaternium-15, glutaraldehyde	+ 12	Corticosteroids, cosmetics, dietary, emulsifier, fragrance, sunscreen	Quaternium-15						
9	– 85	NACDG	NACDG: dimethylaminopropylamine, neomycin, cocamidopropyl betaine, oleamidopropyl dimethylamine, fragrance mix	– 18	Emulsifier, sunscreen, NACDG	NACDG: glutaraldehyde 1% pet	+ 17	Cosmetics, eye, fragrance	Cosmetics: lauryl polyglucose 3% pet, octyl gallate 0.25% pet, phenyl salicylate (salol) 1% pet Eye: neomycin sulfate 20% pet Fragrance: hydroperoxide of linalool 1% pet	+ 19	Emulsifier, NACDG	None
17	– 69	NACDG, sunscreen, corticosteroids	NACDG: budesonide 0.01% pet, alclometasone-17,21-dipropionate 1.0% pet	+ 8	Corticosteroids, cosmetics, emulsifiers, fragrance, sunscreen, NACDG	NACDG: budesonide 0.01% pet Corticosteroids: budesonide 0.01% pet, alclometasone-17,21-dipropionate 1.0% pet Emulsifier: Amerchol L-101 50% pet, lanolin alcohol 30% pet, propylene glycol 30% pet, stearyl alcohol 30% pet, wool alcohols ointment 100% Fragrance: benzyl alcohol 10.0% sof, hydroperoxide of linalool 1.0% pet, hydroperoxide of limonene 0.3% pet, perfume mix						

20	− 2	NACDG, sunscreen	Emulsifier: Amerchol L-101 50% pet, lanolin alcohol 30% pet, wool alcohol ointment 100% Eye medicaments: kanamycin sulfate 10% pet, neomycin sulfate 20% pet Fragrances: eugenol 2.0% pet, Lyral 5.0% pet, citral 2.0% pet, fragrance mix II 14.0% pet, hydroperoxide linalool 1% pet, hydroperoxide limonene 0.3% pet, perfume mix	+ 8	Emulsifier, fragrance, hairdressing, personal	Emulsifier: Amerchol 101 50% pet, decyl glucoside 5% pet, lanolin alcohol 30% pet, Tween 40 10% pet, Tween 80 10% pet, wool alcohols ointment Fragrance: *Narcissus* absolute 2.0 pet, fragrance mix II 14.0% pet, amyl cinnamyl alcohol 5.0% pet, perfume mix Hairdressing: ammonium persulfate 2.5% pet, nickel sulfate hexahydrate 5.0% pet, lauryl glucoside 3.0 pet, oleamidopropyl dimethylamine 0.1% aq, decyl glucoside 5% pet
29	− 5	NACDG, emulsifier, corticosteroid, personal	NACDG: potassium dichromate 0.25% pet, nickel sulfate hexahydrate 2.5% pet, 2-bromo-2-nitropropane-1 3-diol (bronopol) 0.5% pet, thimerosal (Merthiolate) 0.1% pet, cobalt (II) chloride hexahydrate 1% pet, textile dye mix 6.6%, benzoyl peroxide 1% pet, formaldehyde 2% aq Emulsifier: sodium lauryl sulfate 0.5% pet, triethanolamine 2.5% pet	+ 11	Corticosteroids, cosmetics, dietary, fragrance, hairdressing	Hairdressing: ammonium persulfate 2.5% pet, lauryl glucoside 3.0% pet, decyl glucoside
36	− 10	T.R.U.E. TEST	Fragrance mix I, fragrance mix II, carba mix 3.0% pet, Amerchol L-101 50% pet	+ 23	NACDG, emulsifier, fragrance, personal	NACDG: fragrance mix II 14% pet, decyl glucoside 5% pet, benzalkonium chloride 0.1% aq Emulsifier: stearyl alcohol 30% pet Fragrance: Lyral 5% pet, hydroperoxide of limonene 0.3% pet

(Continued on next page)

TABLE 4. *(Continued)*

Patch Test 1 (Months Before [–] Starting Dupilumab)	Series Tested	PT 1 Positives	PT 2 Date (Months Before [–] or After [+] Starting Dupilumab)	Series Tested	PT 2 Positives	PT 3 Date (Months Before [–] or After [+] Starting Dupilumab)	Series Tested	PT 3 Positives	PT 4 Date (Months Before [–] or After [+] Starting Dupilumab)	Series Tested	PT 4 Positives
63 – 27	NACDG, textile	NACDG: neomycin sulfate 20% pet, bacitracin 20% pet, ethyl acrylate 0.1% pet, glutaraldehyde 1% pet, ammonium persulfate 2.5% pet	+ 6	Fragrance, corticosteroids, cosmetics, emulsifiers, eye medicaments, fragrance, sunscreen	Emulsifier: Amerchol L-101 50% pet, lanolin alcohol 30% pet, wool alcohols ointment 100% Eye medicaments: kanamycin sulfate 10% pet, neomycin sulfate 20% pet Fragrances: eugenol 2.0% pet, Lyral 5.0% pet, citral 2.0% pet, fragrance mix II 14.0% pet, hydroperoxide linalool 1% pet, hydroperoxide limonene 0.3% pet, perfume mix						

aq, aqueous; NACDG, North American Contact Dermatitis Group; pet, petrolatum; PT, patch test.

the morphology of their residual dermatitis was suggestive of ACD. Ten of the 14 patients had previously been patch tested before beginning dupilumab. Thirteen patients (92.9%) patch tested had at least 1 relevant positive patch test result. The remaining 21 patients were not patch tested, either because the pattern of residual dermatitis was not suggestive of ACD (Table 1, group 2) or because their RFDD resolved with dupilumab alone (Table 1, group 3). There was a high index of suspicion for ACD if dermatitis largely cleared except in areas commonly associated with ACD, including the face/eyelids,[14] hands,[15] and perianal/genital area.[16] Patch testing involved the NACDG standard series of 80 allergens,[17] extended patch testing series, and patients' personal products.

A total of 81 positive reactions to 41 individual allergens were detected in 14 patients (Table 2). Only 1 patient of the 14 patients who were patch tested had zero positive results, and the average number of positive patch results was 10. Of note, 50.6% of the positive reactions to allergens were not included on the NACDG standard series and were instead found on ESPT.

Allergens in the emulsifier/surfactant category accounted for the greatest number of positive patch test results within an allergen subclass (n = 15) and accounted for 35.8% of all positive reactions. Fragrances (n = 12) accounted for 37.0% of the total positive reactions. Hydroperoxides of linalool were the most common allergen with 8 positive reactions, accounting for 9.9% of all positive results. Preservatives accounted for the next greatest subclass (n = 7) accounting for 12.3% of all positive reactions. The next most common reactions were to medicaments (n = 4, 8.6% of the total positive reactions). In addition, the patients experienced positive patch test reactions to 43 personal products (Table 3).

Facial Dermatitis After Patch Testing and Allergy Avoidance

At the most recent follow-up appointment (an average of 65.4 weeks after beginning dupilumab), 6 patients (17.6%) who had not experienced FD resolution at the initial follow-up ultimately experienced resolution on dupilumab alone. Of the 14 patients who were patch tested on dupilumab and subsequently avoided allergens, 3 (21.4%) experienced complete resolution of their RFDD. Notably, 7 patients (50%) endorsed being mostly to completely clear of FD, and 12 patients (85.7%) who were patch tested endorsed that patch testing was at least "somewhat" helpful. Of the patients with RFDD after starting dupilumab, 12 (34.3%) and 15 (42.9%) used topical steroid and nonsteroid medications, respectively, to control any residual facial AD. Table 4 lists allergens that were positive in RFDD patients before and after dupilumab, demonstrating the remarkable number of positive patch test results while on dupilumab therapy in this patient population.

DISCUSSION

Dupilumab and FD

Facial dermatitis has been reported to occur in up to 19% of adults[11] and 29% of children[6] with AD during dupilumab treatment.

Although studies do not differentiate[6] or are inconsistent regarding whether the reported FD is residual[7] versus new onset,[2–5,9–11] our study specifically investigated whether FD on dupilumab is residual or new onset. Nearly half of the patients with FD before dupilumab in our study continued to have RFDD, whereas no patients in our study experienced new-onset FD on dupilumab. Most patients with FD and RFDD were female, likely because of the fact that women are more likely to use facial cosmetic products than men. Of note, both male and female patients have higher skin clearance goals if they experience AD involvement of the face or neck,[18] suggesting that resolution of FD is important to patients. Other studies have reported patients discontinuing dupilumab because of dissatisfaction with facial flaring.[5,11]

This study demonstrates the importance of patch testing in patients who do not experience complete resolution of FD on dupilumab. Variable nomenclature has been used to describe FD in patients on dupilumab, including "drug-associated face and neck dermatitis,"[19] "new regional dermatoses,"[11] and "dupilumab facial redness,"[4] implying that dupilumab is the cause of FD. However, our findings that the patients did not experience new-onset FD on dupilumab and many experienced improvement with ESPT during dupilumab treatment suggest that RFDD could be instead a reflection of underlying, alternative pathology. Diagnostic ESPT clarifies whether the RFDD is secondary to endogenous AD versus exogenous ACD.

Potential Endogenous Contributions to FD During Dupilumab Treatment

Several case reports and retrospective studies have reported new-onset or recalcitrant FD after beginning dupilumab. Reported etiologies of endogenous causes of FD while on dupilumab include site-specific treatment failure,[9] hypersensitivity reaction to dupilumab,[9] new-onset rosacea,[5] and hypersensitivity to *Malassezia* species.[4,7]

Quite a few studies discuss the possibility of a *Malassezia* sensitization component contributing to FD observed in patients on dupilumab.[4,6,7,10,19] For example, 1 study reports 2 patients who experienced new-onset FD after starting dupilumab—1 patient had elevated *Malassezia*-specific immunoglobulin E and completely cleared after itraconazole treatment, and 1 patient had negative patch testing and experienced significant improvement after treatment with itraconazole.[4] Of note, patients with AD involving the head and neck region who are not receiving dupilumab have been shown to have positive *Malassezia*-specific immunoglobulin E and skin prick test results,[20] confounding the analysis. In addition, it is important to note that the patients presented in this study by de Beer et al[4] experienced new-onset rather than residual FD, suggesting an alternative etiology to AD, as FD secondary to AD would likely have been present before dupilumab. It is possible that *Malassezia* hypersensitivity has been unmasked by the resolution of FD secondary to AD treated by dupilumab in some patients who experience new-onset FD after starting dupilumab. However, it is less likely that dupilumab itself is responsible for this new-onset FD given that *Malassezia* sensitization is thought to be potentiated by IL-17 and IL-23 signaling induction,[19] and dupilumab reduces T helper 17 pathway activity.[21]

Potential Exogenous Contributions to FD During Dupilumab Treatment

Our study provides evidence for the contribution of underlying ACD to RFDD while on dupilumab for AD. Patients with difficult-to-treat AD often have high rates of concomitant ACD.[22,23] Although some studies have suggested that dupilumab may treat ACD,[24] others have shown that treatment with dupilumab does not dampen the efficacy of patch testing[25] and does not seem to treat ACD given that patients with both AD and ACD have not experienced resolution of their ACD on dupilumab until allergen avoidance.[8,13,26]

Patients with AD may be at an increased risk of concomitant ACD. This is likely because of the fact that patients with AD may have higher rates of contact sensitization due to the extensive use of topical products to treat their inflamed atopic skin and vulnerability to hapten penetration secondary to barrier defects.[27] Our data support this hypothesis given that emulsifiers and surfactants accounted for the largest contributing allergen subclass in our study.

Of note, 69.1% of the patients included in the study were patch tested before initiating dupilumab. No patients experienced new-onset FD after initiating dupilumab in our study, although it has been reported in other studies.[2–5,9–11] Importantly, we had a high predupilumab patch testing rate, which may have provided the opportunity for allergen avoidance before dupilumab. In addition, the average improvement from baseline in our cohort was 78.3% at the first follow-up appointment after beginning dupilumab, suggesting the utility of patch testing and treatment of concomitant ACD in AD patients before beginning dupilumab.

Patch Testing: Facial Involvement While Receiving Dupilumab Treatment

Fourteen patients (40%) with RFDD were patch tested. All but 1 patient had 1 or more positive patch test results, with an average of 10 positives per patient, and 11 (78.6%) patients had 5 or more positive results on patch testing, suggesting high rates of comorbid ACD. Of note, 50.6% of the allergens that produced positive patch test results are not included on the NACDG standard series, demonstrating the importance of ESPT to accurately test for ACD.

Patients with moderate-to-severe AD are continuously exposed to topical preparations and personal products that include emulsifiers and surfactants, and studies have demonstrated that patients with AD have an increased prevalence of ACD to particular allergens, including emollients, surfactants, and topical medicaments.[23] Importantly, half of the positive reactions in our study would have been missed on patch testing had we not performed ESPT. Given that AD patients have likely experienced prolonged exposure to such products in effort to manage the symptoms of their AD, it is particularly important to include patch test panels, such as emulsifiers, surfactants, fragrances, and topical medicaments, during ESPT.

Patients receiving dupilumab treatment may benefit from patch testing include those with worsening or a changing distribution of dermatitis, or a residual pattern suggestive of ACD.[23] Residual patterns suggestive of comorbid ACD include pronounced face and eyelid predominance,[14] as well as hand[15] and genital[16] involvement. Thus, dermatologists should consider comorbid ACD in a patient who clears everywhere else on dupilumab besides any of these regions.

Here, we demonstrate that patients with RFDD and a pattern suggestive of ACD benefit from patch testing and subsequent allergen avoidance, demonstrating that it is inaccurate to assume that FD is an adverse effect of dupilumab. Expanded series patch testing should be offered to patients who experience RFDD to ensure an accurate diagnosis and to allow for elimination of any exogenous components of residual disease.

Limitations

This is a retrospective chart review, with data reflecting nonrandomized, real-world clinical findings. In addition, response to dupilumab was assessed by subjective patient reporting of percent improvement from baseline as opposed to objective assessment using the Global Assessment and Eczema Area and Severity Index.

CONCLUSIONS

Residual FD during dupilumab treatment is common occurring in 43.8% of our AD cohort. Of the patients with RFDD who were patch tested while during dupilumab treatment 78.6% had 5 or more positive reactions, corroborating our hypothesis of concomitant ACD contributing to RFDD in patients during dupilumab treatment. Furthermore, half of the allergens that produced positive patch test results were not included on the NACDG standard series, illustrating the importance of ESPT to accurately rule in/out ACD. Of the patients who were patch tested, 21.4% experienced complete resolution of RFDD with allergen avoidance, demonstrating the value of patch testing in patients who experience RFDD.

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