

Letters

RESEARCH LETTER

Assessment of the Development of New Regional Dermatoses in Patients Treated for Atopic Dermatitis With Dupilumab

Dupilumab targets the interleukin-4 receptor (IL-4Ra) and is used for moderate-to-severe atopic dermatitis (AD). Some patients treated with this therapy develop new regional dermatoses (NRDs),¹⁻³ of which the etiopathogenesis and prevalence are unclear. We conducted a retrospective cohort study to describe the epidemiology, clinical features, and treatment of patients with AD developing NRDs while being treated with dupilumab.

Methods | Following Stanford University School of Medicine institutional review board approval, the Stanford Medicine Research Data Repository was queried for all adults receiving dupilumab for AD prior to November 1, 2018. Clinical data were obtained by medical chart review and informed consent was waived owing to the retrospective nature of the study and deidentified data used. Those with NRDs met all of the following criteria: the eruption must (1) occur in a new anatomic region or be atypical for flares of AD in the anatomic region, (2) be resistant to usual topical treatments used in the anatomic region, (3) occur on uninterrupted dupilumab

therapy, (4) occur following primary therapeutic response, and (5) not be explained by a different entity. New alopecias were excluded.

Results | Of 124 patients identified, 73 (59%) were included for analysis with a median (range) duration of dupilumab therapy of 181 (0-522) days (Table 1). Seventeen (23%) developed NRDs; these individuals were more likely to report childhood AD (100% vs 63%, $P = .002$) and to have autoimmune disease (41% vs 18%, $P = .046$).

Of the 17 individuals with NRDs, 14 had facial involvement and 4 had a history of patch test-confirmed allergic contact dermatitis (ACD) (Table 2). The predominant morphologies were eczematous (12/17) and erythema (4/17). Most (11/17) were treated with topical corticosteroids. Four stopped taking dupilumab owing to NRDs. Patient 11 underwent biopsy, showing rosacea, dermatophytosis and actinic keratosis. Subsequently, improvement with topical terbinafine was noted at follow-up, though the patient reported episodic erythema for several days after subsequent dupilumab injections. Patient 17 had asynchronous eruptions: biopsy of the upper body eruption showed resolving varicella zoster virus infection and was not considered an NRD, although this patient's subsequent lower-body eruption was negative for HSV and VZV DNA by lesional swab and was considered an NRD.

Table 1. Clinical and Demographic Information

Variable	No. (%)			P Value
	Overall (n = 73)	No New Regional Dermatoses (n = 56)	New Regional Dermatoses (n = 17)	
Sex				.25 ^a
Male	39 (53)	32 (57)	7 (41)	
Female	34 (47)	24 (43)	10 (59)	
Age, median (range), y	42 (18-93)	43 (19-93)	40 (18-55)	.53 ^b
Race				.41 ^c
White	32 (44)	23 (41)	9 (53)	
Asian	23 (32)	20 (36)	3 (18)	
Other	18 (25)	13 (23)	5 (29)	
Childhood atopic dermatitis	52 (71)	35 (63)	17 (100)	.002 ^c
Childhood asthma	26 (36)	18 (32)	8 (47)	.26 ^a
Childhood allergic rhinosinusitis	27 (37)	20 (36)	7 (41)	.68 ^a
Family history of atopy	31 (42)	25 (45)	6 (35)	.50 ^a
Autoimmune history	17 (23)	10 (18)	7 (41)	.046 ^a
History of clinical allergic contact dermatitis	16 (22)	12 (21)	4 (24)	1.0 ¹
Negative patch testing ^d within 2 y prior to starting dupilumab	2 (3)	0 (0)	2 (12)	Test not performed
Conjunctivitis on therapy	11 (15)	8 (14)	3 (18)	.71 ¹
Total length of follow-up, median (range), d	194 (0-522)			
Duration of dupilumab therapy, median (range), d	181 (0-522)			

^a χ^2 test.

^b Wilcoxon rank sum test.

^c Fisher exact test, used because at least 1 cell count was 5 or fewer.

^d Patch testing performed to the American Contact Dermatitis Society Core Allergens (80 allergens) plus supplemental allergen series.

Table 2. Characteristics of Patients With New Regional Dermatoses (n = 17)

No./Sex/Age Range, y	Site	Morphology	Treatment	Days Until Improvement	Stopped Dupilumab Owing to New Dermatoses	Childhood Atopic Dermatitis	Autoimmune History	History of ACD Confirmed by Relevant Patch-Test Reactions	Biopsy Performed
1/F/30-40	Eyelids	Eczematous	Ocular tobramycin, dexamethasone	345	No	Yes	No	Yes	No
2/M/30-40	Hands and feet	Dyshidrosiform	Topical CS, AH	53	No	Yes	Kikuchi disease, rheumatoid arthritis	No	No
3/F/30-40	Face, neck, and chest	Urticarial	Topical CS, CNI	86	Yes	Yes	Ulcerative proctitis	No	No
4/F/50-60	Face	Eczematous	Topical CS, CNI, sunscreen	99	No	Yes	SLE	Yes	No
5/F/40-50	Face, trunk, and thighs	Eczematous	Unspecified	137	Yes	Yes	No	No	No
6/M/20-30	Face	Eczematous	Topical CS	2	No	Yes	No	No	No
7/M/30-40	Face	Eczematous	Emollient	80	Yes	Yes	No	No	No
8/F/18-20	Unspecified	Unspecified	Coconut oil, oatmeal baths	Unspecified	Yes	Yes	No	No	No
9/F/50-60	Eyelids and nasolabial folds	Eczematous	Oral CS	55	No	Yes	Vitiligo, alopecia universalis	No	No
10/M/30-40	Face	Erythema	Topical CS, crisaborole	112	No	Yes	No	No	No
11/M/50-60	Face	Eczematous, erythema	Topical terbinafine, sunscreen	45	No	Yes	No	Yes	Yes
12/F/40-50	Eyelid and periocular	Eczematous	Topical CS	117	No	Yes	No	No	No
13/F/40-50	Forehead	Eczematous	Topical CS, antifungal	112	No	Yes	Hashimoto thyroiditis	No	No
14/F/20-30	Face	Eczematous, erythema	Topical CS, emollient	94	No	Yes	Sjogren syndrome, alopecia universalis	No	No
15/M/40-50	Face	Eczematous, erythema	Topical metronidazole, topical CNI, sunscreen	New ^a	No	Yes	No	No	No
16/F/50-60	Face	Eczematous	Topical CS, mupirocin, bleach baths	None ^b	No	Yes	No	No	No
17/M/50-60	Upper chest and back ^c	Papular, erosions	Topical CS, topical clindamycin, topical CNI, bleach baths, oral antibiotics	43	No	Yes	HLA-B27+ arthritis, IgG3 deficiency	Yes	Yes
	Upper legs and buttocks	Papular, erosions	Topical CS, bleach baths	New ^a					No

Abbreviations: ACD, allergic contact dermatitis; AH, antihistamines; CNI, calcineurin inhibitors; CS, corticosteroids.

^a New regional dermatosis was reported at the most recent follow-up visit.

^b No improvement at 30 days (end of follow-up).

^c In this patient, the upper chest and back eruption was not considered a new regional dermatosis owing to evidence of varicella zoster virus on biopsy. Workup of the upper leg and buttock eruption for herpes simplex or zoster viral infection revealed negative results.

Discussion | In this cohort of 73 adults taking dupilumab for AD, 17 (23%) developed NRDs, with predilection for facial site (14/17) and eczematous morphology (12/17). Most NRDs were treated with topical corticosteroids (11/17) with a median (range) of 94 (2-345) days until documented improvement.

New facial dermatitis while taking dupilumab is suspected to represent unrecognized ACD³ for which the diagnostic utility of patch testing has been recently highlighted.¹ A case series² of patients with ACD revealed that 73% developed facial cutaneous eruption while receiving therapy, a rate several fold higher than in this study. These observations raise the possibility of unrecog-

nized ACD unmasked by differential suppression of ACD elicitation by IL-4 and/or IL-13 inhibition depending on the culprit allergen.² In IL-4 knockout mice, attenuation of ACD to 2,4-dinitrochlorobenzene but not oxazolone has been observed.⁴

However, ACD is unlikely to explain all cases—2 individuals with negative results on comprehensive patch testing performed within 2 years prior to dupilumab initiation developed NRDs. Though ACD to uncommon, untested allergens is possible, we hypothesize that NRDs may represent unmasking of a primary dermatosis in an altered cutaneous immune milieu: unopposed activation of helper T cell subtype 1 (T_H1) and/or T_H17

signaling may flare rosacea,⁵ possibly explaining the facial erythema seen in 4 patients, one of whom had biopsy-proven rosacea. The recurrent erythema with injections seen in Patient 11 is particularly suggestive of rosacea, possibly via an augmented reaction to Demodex via T_H1/T_H17 pathways.⁶

We report clinical characteristics of a retrospective cohort of adult patients with AD developing NRDs while taking dupilumab. Emerging reports suggest a potential role of unrecognized ACD, though larger studies involving biopsy and patch testing are needed to better define the subset of patients to which this pertains.

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Accepted for Publication: January 13, 2019.

Published Online: May 1, 2019. doi:[10.1001/jamadermatol.2019.0109](https://doi.org/10.1001/jamadermatol.2019.0109)

Author Contributions: Drs Zhu and Honari had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Disclosures: None reported.

Funding/Support: The project was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1 TRO01085.

Role of the Funder/Sponsor: The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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