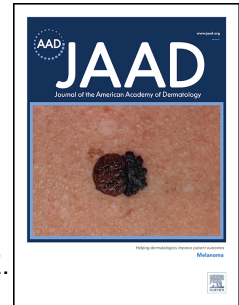


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Diagnostic Testing of Eczematous Dermatitis with Incomplete Response to Dupilumab

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February 5, 2022

Dirk M. Elston, MD
Editor, Journal of the American Academy of Dermatology
Medical University of South Carolina
Charleston, South Carolina

Dear Dr. Elston,

We are submitting our manuscript “Diagnostic Testing of Eczematous Dermatitis with Incomplete Response to Dupilumab” for your consideration as a research letter for publication in the Journal of the American Academy of Dermatology.

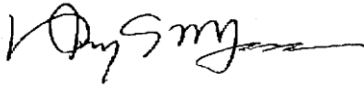
Since the release of dupilumab in March 2017, dermatologists have been using dupilumab to treat moderate to severe adult atopic dermatitis (AD). Providers have experienced mixed results for their patients on dupilumab therapy, with some patients experiencing a complete resolution of the dermatitis, while others noting a persistent residual dermatitis or even a lack of response to dupilumab.

In June 2021, Drs. Narla, Silverberg, and Simpson published an article online in the JAAD suggesting potential diagnostic testing in the setting of an incomplete response to dupilumab in order to unmask alternative and/or concomitant diagnoses (Narla S, Silverberg JI, Simpson EI. Management of inadequate response and adverse effects to dupilumab in atopic dermatitis. Journal of American Academy of Dermatology. <https://doi.org/10.1016/j.jaad.2021.06.017>). In this vein, we examined the charts of 233 patients and identified 50 patients who were incomplete responders to dupilumab, defined by less than 80% improvement during the first 3 to 6 months of therapy. We then detailed the diagnostic testing that was performed as a result of an incomplete response to dupilumab. We also created a framework for the diagnostic testing dermatologists can consider in evaluating patients with an incomplete response to dupilumab. We believe this framework will maximize the chance of successful clearance of AD with dupilumab by identifying potential concomitant disease, given that eczematous dermatitis in adults is often multifactorial.

The submitted manuscript is not under consideration by another publication. The author(s) have no proprietary or commercial interest regarding any materials discussed in this article. Dr. Murase has participated in Advisory Boards for Genzyme/Sanofi, Eli Lilly, LeoPharma, Dermira and UCB, participated in disease statement management talks for Regeneron and UCB, and provided dermatologic consulting services for UpToDate. This research did not receive any funding in the public, commercial, or not-for-profit sectors.

Thank you for your consideration our work for publication in the Journal of the American Academy of Dermatology.

Sincerely,



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Diagnostic Testing of Eczematous Dermatitis with Incomplete Response to Dupilumab

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Keywords: dermatology, atopic dermatitis, allergic contact dermatitis, patch testing, dupilumab, polymorphous light eruption, photodermatitis, cutaneous lupus

To the editor:

Introduction

Dupilumab is a human monoclonal antibody approved to treat adult moderate-to-severe atopic dermatitis (AD). Treatment resistance of AD is defined as a lack of response to therapy despite compliance to the prescribed treatment, and potential diagnostic testing has been suggested to identify alternative or concomitant diagnoses in cases where there is an incomplete response to dupilumab¹⁻⁴. We report the results of diagnostic testing for 50 patients with an incomplete response to dupilumab, who were prescribed dupilumab for a presumed diagnosis of AD, and provide guidance for the management of eczematous dermatitis non-responsive to dupilumab.

Methods

This study involved retrospective data collection from medical records and was approved by the University of California, San Francisco, Institutional Review Board. Inclusion criteria consisted of incomplete response to dupilumab defined by less than 80% patient-reported improvement of total body surface area during the first 3 to 6 months on dupilumab. A retrospective chart review of 233 patients on dupilumab was performed, where 50 patients were classified as incomplete responders to dupilumab. The following comorbid or alternative diagnoses were identified based on diagnostic testing: allergic contact dermatitis (ACD) (n=47), parapsoriasis or psoriasis (n=3), polymorphous light eruption (PMLE) (n=8), cutaneous lupus and mixed connective tissue disease (MCTD) (n=4), lymphoma (n=1), tinea (n=1), scabies (n=1), Netherton syndrome (n=1), and diffuse urticarial and eczematous eruption associated with systemic inflammation (n=1). Out

of the 50 patients, 18 patients were diagnosed with comorbid ACD and an additional alternative condition.

Results

Patient demographics, necessity for further diagnostic testing, areas of residual dermatitis on dupilumab, and the results of diagnostic testing are outlined in Table 1. Patch test series and test results are detailed in Supplemental Tables 1 and 2.

Patients who reported photosensitivity on dupilumab were diagnosed with PMLE, cutaneous lupus, or MCTD. All patients reported at least some history of photosensitivity prior to initiating dupilumab. Patients continued to have photosensitivity after the medication was discontinued, and there were no patients for whom photosensitivity was attributed directly to dupilumab.

Dupilumab does not appear to treat concomitant photosensitive dermatitis. Out of 233 patients evaluated, the only two patients who experienced joint pain as a side effect on dupilumab were diagnosed with cutaneous lupus or MCTD.

Discussion

Upon evaluation of cases with incomplete or lack of response to dupilumab, morphology and location of residual dermatitis and patient history played a significant role in determining appropriate diagnostic testing. All 50 patients with incomplete or lack of response to dupilumab had concomitant conditions or entirely different diagnoses, 38 of whom had a delay in this diagnosis by an average of 12.8 months. Interestingly, 94% of patients had at least one contact allergen identified. Patients diagnosed with AD who fail or incompletely respond to dupilumab should be evaluated for concomitant conditions that may be responsible for the residual

dermatoses. Early identification may improve the clearance rate resulting in faster resolution. We provide the results of evaluating patients with residual dermatitis in Figure 1. Limitations to this study include retrospective design and subjectivity of patient reported clearance.

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FIGURE LEGENDS

Figure 1. Diagram detailing the diagnostic algorithm used when evaluating the 50 AD patients with an incomplete response to dupilumab among 233 patients placed on dupilumab.

Table 1. Summary of patient demographics, mean time on dupilumab, necessity for further diagnostic testing, mean time from dupilumab initiation to diagnostic testing, areas of residual dermatitis on dupilumab, and the results of the diagnostic testing.

*Patients with ACD as the sole concomitant diagnosis with AD were included (29/47 patients); those with an additional alternative diagnosis were excluded so as not to confound reporting of the study results.

**Not all patient information was available to analyze time from dupilumab initiation to diagnosis.

Supplemental Table 1. Patch test series used to diagnose allergic contact dermatitis and positive allergens identified in the study cohort..

Supplemental Table 2. Positive allergens identified in the study cohort. Relevance was defined by verifying a positive patch test allergen as a contributor to the patient's clinical findings and history. Relevance was further scored by definite = A, probable = B, possible = C, past = D (caused dermatitis in the past, but of no current relevance), and unknown = E (no known exposure) in accordance with the North American Contact Dermatitis Society.⁵

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Table 1.

Diagnosis (n)	Mean Age	Gender		Mean time on dupilumab In months	Time from dupilumab initiation to diagnosis In months		Further Diagnostic Testing	Journal Pre-proof on dupilumab %		g %		Biopsy (H&E) % (number of positive tests/total number of patients tested)	
		Female	Male										
Allergic Contact Dermatitis (n=47)*	46.1	69.0% (20/29)	31.0% (9/29)	23.8	14.9 (26/29)**	Dry or pruritic eyes (4), Dry skin (1), Injection site reaction (2)	Residual dermatitis on dupilumab or no response to dupilumab	Scalp Face Eyelids Neck Trunk Hands Upper extremities Lower extremities Genitals	6.9% (2/29) 51.7% (15/29) 24.1% (7/29) 24.1% (7/29) 37.9% (12/29) 13.8% (4/29) 34.5% (10/29) 31.0% (9/29) 3.4% (1/29)	Patch Testing (See Supplemental Table 1)	100.0% (29/29)	Spongiotic dermatitis Spongiotic dermatitis with eosinophils Spongiotic dermatitis with neutrophils Spongiotic dermatitis with lymphocytes Spongiotic psoriasiform dermatitis	26.7% (4/15) 33.3% (5/15) 6.7% (1/15) 6.7% (1/15) 26.7% (4/15)
Parapsoriasis/ Psoriasis (n=3)	49	100% (3/3)	0.0% (0/3)	3.0	1.5 (2/3)**	Dry eyes (2)	Residual dermatitis (plaques) on dupilumab	Trunk Hands Foot	33.3% (1/3) 33.3% (1/3) 66.7% (2/3)	Biopsy H&E	100% (3/3)	Psoriasiform dermatitis with eosinophils Spongiotic dermatitis	33.3% (1/3) 66.7% (2/3)
Polymorphous Light Eruption (n=8)	41.5	62.5% (5/8)	37.5% (3/8)	7.8	13.8 (4/8)**	Dry eyes (2)	Dermatitis in a photosensitive distribution on dupilumab, worsens with sun exposure	Face Neck Hands Upper trunk Upper extremities	75.0% (6/8) 50.0% (4/8) 37.5% (3/8) 12.5% (1/8) 12.5% (1/8)	Anti-nuclear antibody (ANA) Biopsy with Direct immunofluorescence (DIF) Anti-dsDNA antibody Phototesting	(-) 100% (7/7) (-). 100% (3/3) (+) 100% (2/2) (-) 100% (2/2)	Spongiotic dermatitis Psoriasiform dermatitis	42.9% (3/7) 57.1% (4/7)
Cutaneous lupus & Mixed connective tissue disease (n=4)	57	100.0% (4/4)	0.0% (0/4)	24.0	1.4 (2/4)**	Joint pain (2)	Dermatitis in a photosensitive distribution on dupilumab, worsens with sun exposure	Face Eyes Neck Trunk Upper extremities Lower extremities Hands	75.0% (3/4) 25.0% (1/4) 50.0% (2/4) 25.0% (2/4) 75.0% (3/4) 25.0% (1/4) 75.0% (1/4)	ANA (1:80 speckled, 1:320, 1:2560) Biopsy with DIF Anti-smith RNP antibody Anti-centromere antibody Anti-SSA antibody	(+) 100% (4/4) (+) 33.3% (1/3) (-) 66.7% (2/3) (+) 25.0% (1/4) (+) 25.0% (1/4) (+) 25.0% (1/4)	Spongiotic dermatitis Vacuolar interface and perivascular dermatitis Discoid lupus Acantholytic dyskeratosis Lichen simplex chronicus with eosinophils	75.0% (3/4) 50.0% (2/4) 25.0% (1/4) 25.0% (1/4) 25.0% (1/4)
Lymphoma (n=1)	74	0.0% (0/1)	100.0% (1/1)	5.0	4	None	No response to dupilumab, atrophic plaques	Face Body		Biopsy H&E		T-cell receptor delta-expressing epidermotropic T-cell lymphoma	
Systemic contact dermatitis (n=1)	57	0.0% (0/1)	100.0% (1/1)	18.0	17	None	Appearance of dermatitis on dupilumab with supplement/ medication exposure (high dose vitamin B12 due to cobalt allergy)	Upper trunk Upper extremities		Trial off supplement or medication		N/A	
Tinea pedis (n=1)	21	0.0% (0/1)	100.0% (1/1)	12.0	15	None	Residual dermatitis on dupilumab	Feet		KOH: hyphae		Spongiotic dermatitis	
Scabies (n=1)	71	100.0% (1/1)	0.0% (0/1)	2.0	4	None	No response on dupilumab	Nipples Trunk Upper extremities		KOH: scabies		Spongiotic dermatitis	

							Daily pruritus and burrows	Lower extremities		
Netherton syndrome (n=1)	68	100.0% (1/1)	0% (0/1)	9.0	N/A	None	Residual dermatitis on dupilumab, geographic plaques with scale at margin of erythema	Trunk Upper extremities Lower extremities	KOH (-) SPINK5 (+)	Psoriasiform dermatitis Spongiotic dermatitis with eosinophils Perivascular dermatitis with eosinophils
Diffuse urticarial and eczematous eruption associated with systemic inflammation (n=1)	22	100% (1/1)	0% (0/1)	14.0	N/A	None	No response to dupilumab, diffuse eczematous and urticarial plaques	Face Neck Trunk Upper extremities Lower extremities	CU index 38.4 IgE 1768 CRP 63 ESR 38 Periodic Fever Syndrome panel (-)	Perivascular inflammation and rare intravascular neutrophils Spongiotic dermatitis Spongiotic dermatitis with eosinophils

Supplemental Table 1

Allergic Contact Dermatitis (n=47)	
Patch test series	NACDG (43) TRUE (8) Corticosteroid (23) Cosmetics (13) Dietary (11) Emulsifiers (34) Eye Medicaments (2) Fragrance (38) Hairdressing (4) Metal (2) Methacrylate (1) Rubber (1) Sunscreen (11) Textile (4) Personal Products (495)
Positive allergens	Adhesives, Plastics, Resins (9) Anesthetics (3) Antibiotics & Antiseptics (12) Antioxidant (2) Corticosteroids (6) Dietary Additive (1) Emulsifiers & Surfactants (57) Fragrance, Essential Oils, Plant Extracts (102) Hairdressing (9) Metals (35) Preservatives (46) Rubber (10) Sunscreen (5) Textile (7) Topical Medication (1)

Supplemental Table 2

Allergic Contact Dermatitis (n=47)					
Positive allergens (n) & Relevance	Adhesives, Plastics, Resins: 4-tert-Butylphenolformaldehyde resin (2) E Colophony (1) E Dimethylol dihydroxy ethylene urea (1) E Ethyl acrylate (2) C Ethyl cyanoacrylate (1) E Methyl methacrylate (1) E p- Phenyl salicylate E Anesthetics: Caine mix (2) D Dibucaine hydrochloride (1) D Antibiotics & Antiseptics: Bacitracin (7) A Neomycin sulfate (4) A Chloroxylonol (1) D Antioxidant: Butylhydroxyanisole (2) E Corticosteroids: Acloemtason-17 21-dipropiate (2) A Budesonide (2) A Tixocortol-21-pivalate (2) A Dietary Additive: Sorbic acid (1) C	Emulsifiers & Surfactants: Amerchol L101 (6) A Amidoamine (1) A Cetylstearylalcohol (1) A Cocamidopropyl betaine (5) A Coconut diethanolamine (1) A Decyl glucoside (11) A Dimethylaminopropylamine (1) A Dodecyl gallate (2) A Lanolin alcohol (3) A Lauryl glucoside (4) A Lauryl polyglucose (2) B Oleamidopropyl dimethylamine (3) A Propylene glycol (5) A Sodium lauryl sulphate (3) A Stearyl alcohol (3) A Tocopherol (2) A Tween 40 (2) B Tween 80 (2) B	Fragrance, Essential Oils, Plant Extracts: Alpha-isomethyl ionone (1) B Amyl cinnamyl alcohol (1) B Anise alcohol (1) B Balsam of Peru (5) B Benzyl alcohol (1) B Cananga oil (1) C Cinnamic alcohol (2) B Citral (2) B Compositae mix II (2) B D-Limonene (2) A Evernia durfuracea (1) B Eugenol (2) B Fragrance mix I (12) B Fragrance mix II (10) B Geranium oil (1) B Hydroxyisohexyl 3-Carboxaldehyde Lyrall (1) B Hydroxyperoxides of limonene (18) A Hydroperoxides of linalool (18) A Isoeugenol (2) B Jasmine absolute (1) B Lavender absolute (2) A Linalool synthetic (1) A Majanthole (1) B Narcissus absolute (2) B Perfume mix (9) B Sandalwood oil (1) B Ylang-ylang oil (2) B	Hairdressing: Ammonium persulfate (4) C Glyceryl monothioglycolate (2) E p-Phenylenediamine (3) A Metals: Cobalt (II) chloride hexahydrate (8) E Gold (I) sodium thiosulfate dihydrate (3) E Indium (III) chloride (1) E Manganese chloride (1) E Nickel sulfate hexahydrate (7) D Potassium dichromate (6) D Stannous chloride (1) D Thimerosal (6) E Titanium (III) decahydrate (1) E Vanadium (III) chloride (1) E Preservatives: 2-Bromo-2-nitropropylene-1,3-diol (3) C Benzalkonium chloride (5) A Diazolidinyl urea (2) A DMDM hydantoin (1) A Ethylenediamine dihydrochloride (2) C Formaldehyde (2) B Glutaraldehyde (7) E Iodopropynyl butyl carbamate (5) A Methyldibromo glutaronitrile/phenoxyethanol (1) C Methylisothiazolinone (7) A Methylisothiazolinone/Methylchlorisothiazolinone (6) A Octyl gallate (1) B Paraben mix (1) B Quaternium-15 (2) B Sodium benzoate (1) C	Rubber: Carba mix (3) E Diphenylguanidine (2) E Mercaptobenzothiazole (1) E Mercapto mix (1) E Thiuram mix (3) E Sunscreens: Benzophenone-3 (2) A Benzophenone-4 (1) A Methylene bis-benzotriazolyl tetramethylbutylphenol (1) B Sulisobenzene (1) A Textile: Disperse blue 106/124 mix (2) C Textile dye mix (5) C Topical Medication: Benzoyl peroxide (1) D

