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Reid A. Waldman, MD, Madeline Dewane, BA, Steven B. Sloan, MD, Jane M. Grant-Kels, M.D.



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Characterizing Dupilumab Facial Redness: A Multi-institution Retrospective Chart Review

Reid A. Waldman, MD¹, Madeline Dewane, BA¹, Steven B. Sloan², MD, Jane M. Grant-Kels, M.D.¹

¹University of Connecticut Department of Dermatology, Farmington, CT 06032

²Newington, Connecticut VA Department of Dermatology

Corresponding Author:

Steven B. Sloan, M.D.

21 South Road

Farmington, CT 06032

Steven.sloan@va.gov

Tel: 860-679-4600

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Reprint Requests:

Steven B. Sloan, M.D.

21 South Road

Farmington, CT 06032

Steven.sloan@va.gov

Tel: 860-679-4600

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ACCEPTED MANUSCRIPT

Dupilumab facial redness (DFR), (ie, development of eczematous facial rash after initiation of dupilumab) is an adverse event (AE) not described in the dupilumab atopic dermatitis (AD) clinical trials (Figure 1a, 1b, 1c – Online Only. Available at <https://data.mendeley.com/datasets/tnd894mj8m/1>).¹ Although it has only been described in a few case studies, we have encountered DFR with unexpected frequency prompting a retrospective chart review to characterize this AE.^{2,3}

The UConn Health and Connecticut VA medical records were queried for patients receiving dupilumab. Patients were excluded if they were (1) receiving dupilumab for non-dermatologic indications (2) lacking a dermatology follow-up after initiation of dupilumab; and/or 3) not taking the prescribed dupilumab.

Patient demographics, indication for treatment, dosing, and AEs were recorded (Table 1).

111 patients receiving dupilumab for 11 indications included 85 patients receiving dupilumab for AD compared to 26 patients receiving dupilumab for other reasons. 11 patients developed DFR (9.9%). Of these, 9 were receiving dupilumab for AD and 2 for dyshidrotic eczema. Presence or absence of atopy was not significantly related to DFR development (χ^2 testing, $p = 0.7353$). 3/10 patients with facial redness and 21/100 patients without facial redness developed concomitant dupilumab ocular surface disease (DOSD). No significant association between facial redness and DOSD was identified (χ^2 testing, $p = 0.6877$).

Our experience indicates DFR occurs at a much greater frequency than previously reported, often by the time of a patient's two-month follow up visit after drug initiation. We also report two cases of DFR occurring in non-atopic patients. Despite the frequency with which DFR occurs, all 11 patients that developed DFR continued dupilumab at their most recent follow-up suggesting that DFR is less bothersome to patients than their underlying skin condition. Although DFR has been anecdotally associated with DOSD, our analysis did not find this association to be statistically significant.⁴

Four theories have been proposed to explain DFR. DFR may represent a 1) hypersensitivity reaction to dupilumab; 2) site-specific treatment failure; 3) seborrheic dermatitis-like reaction to facial *Malassezia* sp; and/or, 4) paradoxical flaring of allergic contact dermatitis (ACD). Table 2 lists supporting and refuting evidence for each theory. Due to the paucity of biopsy data and reports of successful treatment of DFR, a clear pathogenesis has not been established. We do not have biopsy or patch test data for our patients but suspect that DFR represents a paradoxical flaring of ACD (although inadequate evidence exists to rule out a seborrheic dermatitis-like reaction). Therefore, our approach is to treat empirically for a seborrheic dermatitis-like reaction with topical ketoconazole 2% cream twice daily for two weeks with a plan to patch test all non-

73 responders. Importantly, we do not believe DFR is a hypersensitivity reaction as all of
74 our patients continued on dupilumab without progressing to a generalized
75 hypersensitivity reaction.

76 Study limitation include its retrospective nature, risk of misclassification bias, and
77 lack of clinical photography for all patients. Larger, multi-institutional studies are
78 needed to further evaluate these findings. Our study suggests that DFR is an
79 underappreciated adverse effect of dupilumab that is not associated with DOSD.

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Table 1: Patient Demographics

Variable	Patients with Dupilumab Facial Redness (%)	Patients without Dupilumab Facial Redness (%)
<i>Sex</i>		
Female	4 (9)	41 (91)
Male	7 (11)	59 (89)
<i>Age</i>		
< 18	3 (33)	6 (66)
19-30	2 (12.5)	14 (87.5)
31-44	3 (18)	14 (82)
45-59	2 (7)	28 (93)
60-75	1 (4)	24 (96)
> 75	0 (0)	14 (100)
<i>Dosing Frequency</i>		
Every Other Week	8 (8)	82 (92)
Weekly	2 (22)	7 (78)
Monthly	1 (50)	1 (50)
<i>Drug Indication</i>		
Atopic Dermatitis	9 (11)	76 (89)
Chronic Actinic Dermatitis	0 (0)	2 (100)
Dyshidrotic Eczema	2 (18)	9 (82)
Prurigo Nodularis	0 (0)	2 (100)
Psoriasisiform Dermatitis	0 (0)	3 (100)
Other (Diagnosis with less than 2 patients)	0 (0)	8 (100)
<i>Other Adverse Effects</i>		
Urticaria	0 (0)	1 (100)
Erythema Nodosum	0 (0)	1 (100)
Other Regional Dermatitis	0 (0)	2 (100)
Oral Blisters	0 (0)	1 (100)

Recurrent Sinusitis	0 (0)	1 (100)
Dupiluma b Ocular Surface Disease	3 (13)	21 (87)

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Table 2: Prevailing Theories for the Pathogenesis of Dupilumab Facial Redness		
Theory	Supporting Evidence	Refuting Evidence
Hypersensitivity Reaction	Some patients report non-facial regional flaring Occurs in patients with dyshidrotic eczema and atopic dermatitis It is seen at a higher frequency with more frequent dosing	All patients remained on dupilumab without progression to generalized hypersensitivity reaction
Site-specific Failure	Site-specific failure is known to occur in psoriasis patients receiving biologics	Occurs in patients with dyshidrotic eczema (likely rules out this theory) Occurs in patients with atopic dermatitis that have never had facial involvement (i.e. patients report clear development of facial rash after initiation of the medication) It is seen at a higher frequency with more frequent dosing
Seborrheic Dermatitis-like	Occurs in seborrheic areas Case within our series cleared with topical ketoconazole	Some patients report non-facial regional flaring Facial flaring does not exclusively affect classic 'seborrheic' areas

	It is seen at a higher frequency with more frequent dosing	Does not demonstrate response to topical corticosteroids or topical calcineurin inhibitors
Allergic Contact Dermatitis	A literature review identified a case series of 3 patients who cleared after allergen identification and removal published in JAAD Case Reports Paradoxical worsening of ACD in patients receiving dupilumab could be accounted for by promotion of a TH1 response in otherwise TH2 predominant individuals via dupilumab-induced blockade of IL-4 and IL-13 The opposite reaction (reversal from TH1 to TH2) has been described in psoriasis patients receiving biologics It is seen at a higher frequency with more frequent dosing	Unclear why only the face would be involved Does not demonstrate response to topical corticosteroids or topical calcineurin inhibitors

Figure 1a, 1b, and 1c: Patient with Dupilumab Facial Redness (available online on Mendeley)

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