

Letters

RESEARCH LETTER

Development or Exacerbation of Head and Neck Dermatitis in Patients Treated for Atopic Dermatitis With Dupilumab

The efficacy and safety of dupilumab, a humanized monoclonal antibody targeting the α subunit of the interleukin (IL)-4 and IL-13 receptors, has been assessed in adults with moderate-to-severe atopic dermatitis (AD).^{1,2} Injection site reactions, nasopharyngitis, conjunctivitis, and transient increases in eosinophil counts from baseline were higher in the dupilumab groups than in the placebo groups in pivotal studies.^{1,2} A recent study by Zhu et al³ reported new regional dermatoses in 17 patients with AD treated with dupilumab, with facial area involvement in 14 cases, whereas Blauvelt et al⁴ reported an equal improvement of AD with dupilumab on different anatomic regions in a post hoc analysis of data extracted from 4 phase 3 clinical trials.

Methods | The objective of this study was to describe development or exacerbation of head and neck dermatitis (HN-D) in patients treated for AD with dupilumab. We conducted a national retrospective study among the GREAT network (Groupe de recherche sur l'eczéma atopique de la Société Française de Dermatologie); in accordance with French legislation, institutional review board approval was waived owing to the retrospective review of patient

data for the study; written consent was obtained from each patient. Eligible cases included de novo HN-D (defined as occurrence of HN-D in patients with no particular head and neck involvement at baseline, according to the investigators) (**Figure**) or exacerbation of HN-D (defined as a more than 50% worsening of the eczema signs from baseline on the head and neck area according to the investigators in patients with preexisting HN-D).

Results | Between March 2017 and January 2019, among 1000 adult patients treated for AD with dupilumab, 42 (4.2%) patients with HN-D were included from 29 centers, either HN-D aggravation (n = 32) or de novo occurrences (n = 10).

The patients' clinical characteristics are reported in the **Table**. The average age was 38.6 years (range, 19-67 years); most patients were men (26; 62%) and were diagnosed with AD during infancy or childhood (36; 86%). Among these 42 patients, 18 (43%) had ocular involvement before dupilumab therapy. The HN-D occurred 65.4 days (range, 5-365 days) after initiating dupilumab therapy. Twenty patients (48%) had concomitant ocular adverse effects under dupilumab treatment (mainly conjunctivitis).

Patients with HN-D were treated with topical therapies, including tacrolimus (19/42), steroids (11/42), tacrolimus and steroids (2/42), or antifungal agents (2/42). Systemic

Figure. Head and Neck Dermatitis Exacerbation 1 Month After Dupilumab Therapy Initiation

A Clinical view of the patient's face



B Clinical view of the patient's neck



Table. Clinical Characteristics of the Study Population

Characteristic	Patients, No.		
	Head and Neck Dermatitis		
	Whole Population (n = 42)	Exacerbation (n = 32)	De Novo (n = 10)
Average age, y (median)	38.6 (38.5)	39.1 (38.5)	37.2 (36.5)
Range	19-67		
Male sex, No. (%)	26 (62)	21 (66)	5 (50)
History of AD			
Onset of disease			
Infant	24	19	5
Child	12	9	3
Teenager	3	1	2
Adult	3	3	0
Average duration, y (median)	30.1 (28)	30.5 (28)	28.9 (27.5)
Severity of AD before/after dupilumab therapy, IGA ^a			
0	0/4	0/3	0/1
1	0/21	0/17	0/4
2	2/9	0/6	2/3
3	18/2	14/2	4/0
4	22/4	18/3	4/1
Delay of occurrence of HN-D, d (median)	65.4 (47.5)	72 (44)	60 (32.5)
Ocular involvement before dupilumab therapy (n = 18)			
Conjunctivitis	8	7	1
Blepharitis	0	0	0
Palpebral eczema	3	3	0
Keratitis	2	1	1
Others	5	5	0
Ocular involvement after dupilumab therapy (n = 25)			
Conjunctivitis	11	10	1
Blepharitis	4	2	2
Palpebral eczema	3	3	0
Keratitis	2	1	1
Others	5	4	1
Concomitant HN-D and ocular involvement, No. (%)	20 (48)	16 (50)	4 (40)
Therapy Used for HN-D Treatment			
Antifungal agents			
Topical	2	2	0
Systemic	4	3	1
Steroids			
Topical	11	8	3
Systemic	2	1	1
Topical tacrolimus inhibitors			
Calcineurin	19	16	3
Steroids and calcineurin	2	2	0
Not known	2	0	2
Evolution of HN-D			
Aggravation ^b	8	6	2
Persistence ^c	5	5	0
Improvement ^d	22	16	6
Not known	7	5	2

(continued)

Table. Clinical Characteristics of the Study Population (continued)

Characteristic	Patients, No.		
	Whole Population (n = 42)	Head and Neck Dermatitis	
		Exacerbation (n = 32)	De Novo (n = 10)
Discontinuation of dupilumab therapy (n = 7)			
HN-D involvement	4	3	1
Ocular involvement	1	1	0
HN-D and ocular involvement	1	0	1
Other involvement ^e	1	1	0

Abbreviations: AD, atopic dermatitis; HN-D, head and neck dermatitis; IGA, investigator global assessment.

^a Severity was evaluated with an IGA scale of 5 points: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe.

For 2 patients, IGA after dupilumab was not known.

^b With topical tacrolimus (n = 4), topical steroids (n = 1), topical steroid and topical tacrolimus (n = 1), and systemic antifungals (n = 2).

^c With topical tacrolimus (n = 3) and topical antifungals (n = 2).

^d With topical tacrolimus (n = 12), topical steroids (n = 6), systemic steroids (n = 1), systemic antifungals (n = 2), and unknown (n = 1).

^e For persistent enlarged lymph node involvement.

antifungal agents were used in 4 cases, with total regression of HN-D in 2 cases. An improvement of HN-D was reported in 22 cases, an aggravation in 8 cases, and persistence in 5 cases under these concomitant therapies. Dupilumab therapy had to be discontinued for 5 patients owing to HN-D severity in 4 cases, and to concomitant ocular and HN-D involvement in 1 case.

Discussion | There are several hypotheses to explain these occurrences of HN-D: (1) a flare of AD owing to topical steroid withdrawal during dupilumab therapy; (2) a modulation of T helper (T_H) cell signaling due to IL-4 receptor alpha blockade, unmasking an allergic contact dermatitis; (3) an activation of the T_H17 pathway, leading to a proliferation of *Malassezia* fungus, which is predominantly localized in the sebaceous HN area. Indeed, *Malassezia* may increase AD severity in patients with HN-D.⁵ A recent study reported the implication of the T_H17 pathway in controlling fungal colonization and driving *Malassezia*-induced inflammation in atopy-like skin in a mouse model of *Malassezia* skin colonization.⁶ Moreover, the authors reported a higher frequency of *Malassezia*-responsive memory CD4⁺ T cells among memory T cells from the peripheral blood of patients with AD compared with healthy controls. Interestingly, in the study by Zhu et al,³ of 14 patients with HD treated with dupilumab, 1 patient's AD improved after topical treatment with the antifungal drug terbinafine. These new facial dermatoses could correspond to the HN-D de novo form, with similarities in terms of epidemiological (sex, onset of AD during childhood) and clinical characteristics (facial lesions, efficacy of antifungal treatment).

We report herein a novel adverse event in patients treated with dupilumab therapy for moderate-to-severe AD as de novo occurrence or exacerbation of HN-D. A dysregulation in the balance of the T_H cell signaling pathway by dupilumab could explain this particular localization.

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1. Simpson EL, Bieber T, Guttman-Yassky E, et al; SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348. doi:10.1056/NEJMoa1610020
2. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised,

double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303. doi:10.1016/S0140-6736(17)31191-1

3. Zhu GA, Chen JK, Chiou A, Ko J, Honari G. Assessment of the development of new regional dermatoses in patients treated for atopic dermatitis with dupilumab. *JAMA Dermatol*. 2019;155(7):850-852. doi:10.1001/jamadermatol.2019.0109
4. Blauvelt A, Rosmarin D, Bieber T, et al. Improvement of atopic dermatitis with dupilumab occurs equally well across different anatomical regions: data from phase III clinical trials. *Br J Dermatol*. 2019;181(1):196-197.
5. Darabi K, Hostetler SG, Bechtel MA, Zirwas M. The role of *Malassezia* in atopic dermatitis affecting the head and neck of adults. *J Am Acad Dermatol*. 2009;60(1):125-136. doi:10.1016/j.jaad.2008.07.058
6. Sparber F, De Gregorio C, Steckholzer S, et al. The skin commensal yeast *Malassezia* triggers a type 17 response that coordinates anti-fungal immunity and exacerbates skin inflammation. *Cell Host Microbe*. 2019;25(3):389-403.e6. doi:10.1016/j.chom.2019.02.002