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5 Article type : Letter to Editor

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8 **Title:** Inflammatory alopecia in patients on dupilumab: a retrospective cohort study at an
9 academic institution.

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18 **Manuscript Word Count:** 595/600

19 **Figures:** 1 (maximum 2 total figures and tables)

20 **Tables:** 1 (maximum 2 total figures and tables)

21 **References:** 10/10

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/jdv.16094](https://doi.org/10.1111/jdv.16094)

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2 Email: honari@stanford.edu.

3 **Conflicts of Interest:** None declared.

4 **Source of Funding:** None.

5 **Keywords:** alopecia, atopic dermatitis, dupilumab, adverse effect, immunology,
6 epidemiology

Dupilumab targets IL-4R α and is used for moderate-to-severe atopic dermatitis (AD). Prior reports have described new alopecia areata (AA),¹ flaring of prior AA,² as well as improvement or resolution of AA³ in patients treated with dupilumab. We conducted a retrospective cohort study to describe the natural history of prior or new inflammatory alopecia in patients on dupilumab.

Following institutional review board approval, the Stanford Research Repository was queried for adults with alopecia receiving dupilumab between 1998 and June 1, 2019.

Patients with only androgenetic alopecia were excluded. One patient with suspected trichotillomania was included, as there was overlying dermatitis, and trichotillomania can mimic AA.

Database query yielded 195 adults prescribed dupilumab, of which 29 had a history of alopecia. Of these, 8 (28%) individuals with active or recently active alopecia were included for analysis, with a median (range) duration of dupilumab therapy of 295 (0 – 621) days (Table 1). On dupilumab, two patients (Nos. 1 and 2) had new onset alopecia: one had clinically suspected AA but demonstrated histologic features atypical of AA (Figure 1A-D) and the other had presumed AA with no biopsy performed. Other patients had recurrence of prior resolved AA (No. 3), stable ongoing AA (Nos. 4 and 5), resolution of ongoing AA (No. 6), and resolution of suspected trichotillomania (No. 7). Lastly, one patient had prior resolved AA without recurrence on dupilumab (No. 8).

In this retrospective cohort study of inflammatory alopecia among adults on dupilumab for AD, we describe 2 patients with new AA-like presentations, one of which demonstrated psoriasiform changes on biopsy concerning for a possible drug-induced alopecia. AD and AA are comorbid conditions, and concurrent AD confers increased risk for severe AA.⁴ It is therefore plausible that new AA in this at-risk population is independent of dupilumab therapy. Moreover, the clinical presentation and age at onset of AA in our patients and others¹ is compatible with sporadic AA.

However, the new psoriasiform alopecia in one patient 278 days after dupilumab initiation, which improved following discontinuation of dupilumab (Figure 1A-B), is suspected to be drug-induced. The patient was healthy, with no stigmata of psoriasis and no exposure

1 to TNF-alpha inhibitors. The histologic findings showed marked miniaturization of hair
2 follicles, a pronounced telogen-catagen shift, atrophy of sebaceous lobules, and a
3 perifollicular lymphoplasmacytic infiltrate with occasional eosinophils reminiscent of a TNF-
4 alpha inhibitor induced psoriasiform alopecia (Figure 1C-D). Sebaceous atrophy is not a
5 feature of AA but can be seen in other drug-induced alopecias, including in a patient with
6 suspected dupilumab-induced alopecia.¹ Prior work has demonstrated that IL-4/13
7 antagonize IL-17A⁵ and IL-17A-mediated tight junctions⁶ and antimicrobial peptides,⁷
8 potentially explaining the psoriasiform features seen on dupilumab.

9 Moreover, STAT proteins are known to regulate hair follicle stem cell cycling.⁸ In
10 particular, STAT3 promotes anagen progression in mice and STAT5 promotes hair follicle
11 quiescence.⁸ STAT3 is downstream of IL-4/13, thereby raising the possibility that dupilumab
12 may directly modulate hair follicle cycling via the JAK-STAT pathway. Interestingly, AA
13 patients who responded to topical tofacitinib demonstrated decreased lesional STAT3
14 expression,⁹ suggesting a role for other STAT proteins⁸ or collateral signaling pathways.¹⁰

15 In conclusion, we report the natural history of eight individuals with inflammatory
16 alopecia on dupilumab. Two developed new AA-like alopecia, of which one was considered
17 a putative drug-induced alopecia. As alopecia associated with dupilumab is increasingly
18 reported, characterization of AA-like inflammatory alopecias in these patients with
19 histopathology and immunoprofiling is important. Furthermore, as JAK inhibitors are
20 increasingly used for the treatment of AA and dupilumab for AD, we anticipate more
21 opportunities to study the role of cytokine and JAK-STAT signaling in the pathogenesis of
22 inflammatory alopecias.

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1 Figure 1. Clinical and pathologic features of new biopsy-proven psoriasiform alopecia on
2 dupilumab. Clinical photographs of Patient No. 1 taken (A) several hours following scalp
3 biopsy (435 days after dupilumab initiation) and (B) 206 days after scalp biopsy (241 days
4 after stopping dupilumab). Paraffin-embedded, hematoxylin and eosin stained tissue
5 sectioned (C) longitudinally viewed at 40X and (D) transversely viewed at (C) 40X
6 magnification demonstrate a psoriasiform alopecia with miniaturization of hair follicles, a
7 pronounced telogen-catagen shift, atrophy of sebaceous lobules, and a perifollicular
8 lymphoplasmacytic infiltrate with occasional eosinophils.

Table 1. Clinical and demographic characteristics of patients with history of new or prior inflammatory alopecia on dupilumab, N = 8.

Patient No.	Summary of clinical behavior	Age/ Sex	Site and morphology	Diagnosis	Treatments for alopecia†††	Onset of alopecia	Clinical course of alopecia***	Stopped dupilumab due to alopecia	Duration on dupilumab***	Biopsy done
1	New onset alopecia on dupilumab	31M	Scalp, frontotemporal, localized nonscarring alopecic patch with perifollicular scale†	Psoriasiform alopecia, new	Topical steroids (C)	278 days after dupilumab initiation	Partial improvement	Yes	400 days	Yes
2	New onset alopecia on dupilumab	37M	Right jawline, localized nonscarring alopecic patch†	Alopecia areata, new	Topical calcineurin inhibitors (C)	35 days after dupilumab initiation	No follow up visit*	No	360 days	No
3	Prior resolved alopecia, recurrent on dupilumab	37F	Scalp, occipital, localized alopecic patches†	Alopecia areata, preexisting	Topical steroids (P, C)	Several years prior to dupilumab initiation**	Stable disease	No	286 days	No
4	Prior ongoing alopecia, stable on dupilumab	49F	Scalp, frontal hair line, nonscarring alopecic patches with broken hairs††	Alopecia areata, preexisting	Topical steroids (P), intralesional steroids (P), topical squaric acid (P), oral tofacitinib (P)	2,582 days before dupilumab initiation	Stable disease	No, stopped for suboptimal control of atopic dermatitis	303 days	Yes
5	Prior ongoing alopecia, stable on dupilumab	52F	Scalp and face with generalized alopecia††	Alopecia universalis, preexisting	Oral steroids (P, C), oral tofacitinib (P)	At age 2	Stable disease	No, stopped for conjunctivitis	250 days	No

6	Prior ongoing alopecia, resolved on dupilumab	27F	Scalp, diffuse, with alopecic patches with regrowth of pigmented hair††	Alopecia universalis, preexisting	Intralesional steroids (P, C), oral steroids (P), oral cyclosporine (P), oral hydroxychloroquine (P)	3,515 days before dupilumab initiation	Complete resolution	No	621 days	Yes
7	Prior ongoing alopecia, resolved on dupilumab	25M	Scalp, parietal, localized patch of decreased hair density††	Trichotillomania, preexisting	N-acetylcysteine (C)	59 days before dupilumab initiation	Complete resolution	No	281 days	No
8	Prior resolved alopecia, no recurrence on dupilumab	22F	Scalp, vertex, localized nonscarring alopecic patch with regrowth†	Alopecia areata, preexisting	Topical steroids (P)	2,313 days before dupilumab initiation	Insufficient specialty follow up	No	0 days	No

*No specialty follow up visit following diagnosis of alopecia.

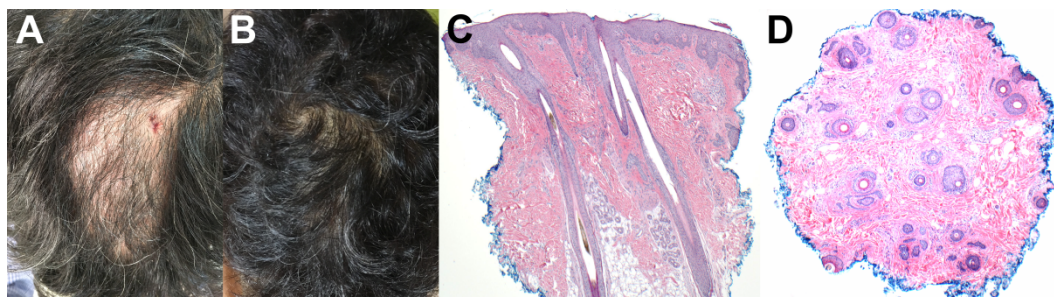
**Unable to further specify date of onset of alopecia.

***Defined as extent of alopecia at most recent specialty follow up compared to maximal extent on dupilumab as assessed by electronic communication, telephone or in-person visit.

†At time of diagnosis.

††At time of dupilumab initiation.

†††(P) denotes prior to dupilumab initiation and (C) denotes concurrent with dupilumab therapy.



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