Dermatology-ophthalmology collaborations are needed in dupilumab-associated ocular events

To the Editor: We read with great interest the article, "Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-weeks results from the Dutch BioDay registry" by Ariëns et al[1] published in the *Journal of the American Academy of Dermatology* in September 2020.

In this prospective multicenter observational longitudinal cohort study, adult patients with treatment-refractory atopic dermatitis (AD) received dupilumab for 52 weeks. The authors reported high treatment response rates; however, conjunctivitis was the most reported adverse event, occurring in 34.1% of participants. Reported risk factors included those with significantly higher Eczema Area and Severity Index scores ($P = .004$) and serum thymus and activation-regulated chemokine levels ($P = .045$).[1] Dupilumab has also been associated with other ocular adverse events, including blepharitis, keratitis, eye pruritus, and dry eyes, which can be collectively referred to as "dupilumab-associated external ocular disorders" (DAEOD). However, these ocular events have not been evaluated by ophthalmologists during phase II and III data collection.

Fostering collaborations between ophthalmology and dermatology could help further characterize DAEOD and guide its management. For reasons not well understood, the incidence of conjunctivitis in dupilumab patients with asthma (0%-2.3%), chronic rhinosinusitis with nasal polyps (1.6%), or eosinophilic esophagitis (0%) is low to none; thus, patients with AD may be particularly susceptible (Table I).[2]

Current hypothesized mechanisms of DAEOD include decreased intraepithelial goblet cells, increased *Demodex* mites in cutaneous and ocular hair follicles, and increased eosinophil levels.[3-5] However, these studies were limited in design, with insufficient ocular subtype characterization and differentiation, and lack of conclusive data on why conjunctivitis has selective affinity for patients with AD.

Most of the current literature is published in dermatology journals; thus, directing DAEOD publications to ophthalmology journals may help target the interests of ophthalmologists. Eye examinations at baseline and for treatment-emergent ocular symptoms are now being implemented in several trial

Table I. Placebo-adjusted percentage of dupilumab associated conjunctivitis[2]

Disease	Trial abbreviation	Trial phase	Dupilumab dose	Placebo-adjusted percentage
CRSwNP	LIBERTY NP SINUS 52/LIBERTY NP SINUS-24	3	300 mg q2w	1.2
EOE	EoE	2	300 mg qw	0.0
Asthma	LIBERTY ASTHMA QUEST	3	200/300 mg q2w*	−1.0
	LIBERTY ASTHMA VENTURE	3	300 mg q2w	0.0
	LIBERTY ASTHMA TRAVERSE	3	300 mg q2w	1.3
AD	LIBERTY AD SOLO CONTINUE~	3	300 mg q8w	−1.3
	LIBERTY AD SOLO CONTINUE†	3	300 mg q4w	−0.3
	LIBERTY AD SOLO CONTINUE†	3	300 mg qw/q2w‡	0.5
	LIBERTY AD PEDS	3	300 mg q4w	2.5
	LIBERTY AD PEDS	3	100/200 mg q2w§	10.6
	LIBERTY AD SOLO 1	3	300 mg qw	4.2
	LIBERTY AD SOLO 1	3	300 mg q2w	5.6
	LIBERTY AD SOLO 2	3	300 mg qw	4.2
	LIBERTY AD SOLO 2	3	300 mg q2w	5.5
	LIBERTY AD ADOL	3	200/300 mg q2w‖	5.1
	LIBERTY AD ADOL	3	300 mg q4w	6.1
	LIBERTY AD CHRONOS	3	300 mg q2w	5.7
	LIBERTY AD CHRONOS	3	300 mg qw	11.4

AD, Atopic dermatitis; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *EOE*: eosinophilic esophagitis; *q#w*, every # week(s).
*Results of 200 mg q2w and 300 mg q2w were reported together in the original article.
†Enrollment criteria included patients from SOLO 1 and 2 who achieved an Investigator's Global Assessment (IGA) score of 0 or 1 or ≥75% improvement in Eczema Area and Severity Index scores (EASI-75) at week 16.
‡Results of 300 mg qw and 300 mg q2w reported together in the original article.
§Dosage was 100 mg if baseline weight was <30 kg and 200 mg if baseline weight was ≥30 kg.
‖Dosage was 200 mg if baseline weight was <60 kg and 300 mg if baseline weight was ≥60 kg.

phases for pipeline medications. Similarly, early referral of high-risk patients for eye examinations may prevent or mitigate DAEOD. High-risk patients include those with existing ocular symptoms, a history of external ocular conditions, and severe AD. In our experience, patients with AD involving the face/periorbital regions also tend to have a higher risk. Early referral and continuous collaborative management have significantly minimized existing ocular conditions and newly developed DAEOD in our patients.

Ultimately, the goal is to safely initiate and continue dupilumab treatment for patients with AD because this is currently the only approved systemic targeted immunomodulating therapy. Those patients who present at their baseline eye examinations with ocular manifestations of AD may then undergo concurrent ocular treatment, which incidentally is similar to DAEOD treatment (lubricant tears, and antihistamine, steroid, and cyclosporin eye drops, etc). Additionally, eye examinations and timing of symptom onset can aid to distinguish DAEOD from primary ocular pathology.

It is important to optimize our approach to these concerns promptly because numerous immunomodulators are emerging. Further investigations characterizing associated adverse ocular events and understanding the pathomechanism of at-risk patients are needed. Additionally, guidelines for proactive diagnosis and management of DAEOD should be established and disseminated to dermatology and ophthalmology literature.

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Conflicts of interest

Dr Shi is a stock shareholder of Learn Health and has served as an advisor, investigator, and/or speaker for Sanofi Genzyme, Regeneron, AbbVie, Burt's Bees, Dermira, Eli Lilly, Novartis, Pfizer, Galderma, LEO Pharma, Sun Pharma, Menlo Therapeutics, GpSkin, and Skin Actives Scientific. Dr Hsiao has served as an advisor for Novartis. Authors Thompson and Yu have no conflicts of interest to declare.

REFERENCES

1. Ariëns LF, van der Schaft J, Spekhorst LS, et al. Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-weeks results from the Dutch BioDay registry. *J Am Acad Dermatol*. 2021;84(4):1000-1009.
2. National Institutes of Health. U.S. National Library of Medicine. ClinicalTrials.gov. Accessed November 17, 2020. Available at: https://clinicaltrials.gov
3. Thyssen JP, Toft PB, Halling-Overgaard A-S, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. *J Am Acad Dermatol*. 2017;77(2):280-286.e1.
4. Bakker DS, Ariens LFM, van Luijk C, et al. Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis. *Br J Dermatol*. 2019;180(5):1248-1249.
5. Thyssen JP. Could conjunctivitis in patients with atopic dermatitis treated with dupilumab be caused by colonization with Demodex and increased interleukin-17 levels? *Br J Dermatol*. 2018;178(5):1220.

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