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COMMENT & RESPONSE

Learning About Dupilumab-Associated Conjunctivitis

To the Editor We read with great interest the Brief Report by Treister et al¹ published in a recent issue of *JAMA Dermatology*. We applaud the authors' initiative to investigate this important topic because practitioners and the public lack sufficient information on the predisposing factors for dupilumab-associated conjunctivitis (DAC).

Dupilumab is a new drug, and we are continuing to learn about its potential and adverse effects. While conjunctivitis was a significant adverse event occurring in 3% to 14% of patients with atopic dermatitis (AD) who received biweekly dupilumab treatments in phase 3 trials (vs <1%-8% in the placebo cohorts),^{2,3} no significant increased risk of conjunctivitis associated with dupilumab was observed in asthma trials (2.3% in the dupilumab cohort vs 3.3% in the placebo cohort).⁴ In dupilumab pivotal trials in AD, conjunctivitis was either patient reported or dermatologist assessed rather than ophthalmologist evaluated.

The discrepancy in adverse event profiles between dupilumab-treated patients with AD vs asthma raises questions regarding certain characteristics unique to patients with AD that increase their susceptibility to developing DAC. In addition to more severe baseline AD, as identified by Treister et al,¹ we speculate that there may be additional predisposing characteristics in the subset of patients who develop DAC. Is head and neck involvement, especially periocular dermatitis, a risk factor? Might these patients have underlying atopic eye conditions such as keratoconus or atopic keratoconjunctivitis? Furthermore, is DAC a paradoxical reaction similar to the head and neck erythema seen with dupilumab treatment?⁵

To address these questions more thoroughly, there is an urgent need for post hoc analysis to compare the characteristics of study participants who developed conjunctivitis with those who did not. Improved understanding of the natural history and more precise diagnostic criteria will help us counsel patients on the risk of DAC. We fully agree with the assertion of Treister et al¹ that identifying at-risk patients will translate into early ophthalmology referral, collaborative care, and perhaps prophylactic treatment. With the use of hydroxychloroquine in treatment of autoimmune dermatoses, we typically recommend annual eye examinations owing to the risk of hydroxychloroquine retinopathy, which has a 7.5% prevalence in patients treated for more than 5 years.⁶ Given the comparable rate of ocular complications in patients with AD receiving dupilumab, we should consider recommendation for

routine eye examinations in our dupilumab medication counseling. We are grateful to have a highly effective medication for patients with AD, but we also recognize a need to fill the knowledge gap in DAC and build communication with our ophthalmology colleagues to promote better information and care for patients with AD treated with dupilumab.

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In Reply We are grateful to Hendricks and Shi for their interest in our recent article.¹ We wholeheartedly agree that the difference in adverse events between those treated for AD vs asthma is striking and warrants deeper investigation. The suggestions that they have offered are insightful and compelling; however, we can address 2 of their specific points about possible underlying keratoconus or allergic conjunctivitis: (1) one of us (C.K.-C.), an ophthalmologist, noted that while formal corneal mapping was not performed, none of the patients appeared to present clinically with keratoconus; (2) all of the patients in our study denied a history of symptoms suggestive of allergic conjunctivitis when asked.

Additionally, since the publication of our article, several reports have been published that add important information. The first, by Bakker et al,² includes corneal biopsies of 6 patients, and the findings were remarkable for a decreased intraepithelial goblet-cell (GC) density as well as a multicellular immune-cell infiltrate, consisting mainly of T cells and eosinophils. The authors suggest that by blocking interleukin-13 (which may stimulate GC production and mucus secretion),

dupilumab may lead to fewer GCs and decreased mucin production, which could affect the tear film and result in conjunctival inflammation.² Importantly, these results do not correspond with the findings of atopic keratoconjunctivitis or allergic conjunctivitis, which often show an increased GC density and increased mucus production, nor do they fit with a diagnosis of ocular rosacea.² A recent article by Yamane et al³ addresses speculation about periocular dermatitis and suggests that this may indeed be associated with the conjunctivitis, at least in some patients, and appears to improve along with the conjunctivitis as the drug reaches undetectable levels.

There is clearly much left to learn, but it is our sincere hope that with both intradisciplinary and interdisciplinary collaboration, great strides in understanding both the disease state as well as this important adverse effect will be made in short time.

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Use of Platelet-Rich Plasma Injection for Rejuvenation of Photoaged Facial Skin?

To the Editor Despite its widespread use for “skin rejuvenation,” there is a surprising paucity of well-controlled, randomized studies of the use of platelet-rich plasma (PRP) in this setting. The study performed by Alam et al¹ is the welcome exception, and they should be praised for the effort. However, we would like to draw attention to 2 issues we think are important to fully understand the study’s conclusions. The authors state that they injected either normal saline or 0.02 mL of PRP per injection site. The sites were approximately 1 cm apart, and injections covered the area of a cheek. They also reported injecting a total of 3 mL of PRP per participant in the study’s treatment arm, which would mean 150 injections per cheek. This number seems too high: an average female cheek accommodates between 80 and 90 injection points if placed 1 cm apart.

Furthermore, the authors state that the results are valuable because “participant-reported outcomes...have increas-

ingly displaced more paternalistic investigator ratings,”^{1(p1451)} citing Reid et al.² In our opinion, when assessing a treatment effect, the approach of self-rating, even if blinded, is not an appropriate method. Study participants by definition cannot be unbiased raters, even if a full blinding is achieved. If in a double-blinded, placebo-controlled study, a primary outcome based on independent, blinded professional assessors fails to find any statistically significant effect of a treatment, then accepting participants’ self-assessment as an equally valuable outcome negates the evidence-based approach and takes us back to the realm of empirical vs anecdotal evidence. Though measures like quality of life may and should be rated by patients themselves, any objective treatment effect should not be assessed and claimed based on the same principle.

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In Reply We appreciate the interest of Drs Pavlović and Loubser in our article.¹ Regarding their first point, that a female cheek may accommodate 80 to 90 injections points rather than 150, we would say that there is substantial variation in cheek size and that the boundaries of the cheek that we specified may be broader than those they equate with the cheek. As the authors appear doubtful, we would like to assure them that we did inject 3 mL of platelet-rich plasma (PRP) into every cheek that was randomized to receive such treatment.

As for their second assertion, that self-rating, even if full blinding is achieved, is not an appropriate measurement method, we would respectfully, strenuously disagree. Even unblinded participant-reported outcomes are widely considered critically important by clinical researchers,² developers of core outcome sets,^{3,4} regulators, and payers.^{5,6} Successful blinding would make such measures at least equivalent to blinded rater measures. In fact, it could be asserted that since individual participants know fine features on their own faces better than any external rater could, participants may be able to detect minute differences not noticeable to a rater. Color and texture are well understood by participants and not esoteric medical markers that only physicians can appreciate. We are unsure what the authors mean when they say that consideration of patient ratings of effect “takes us back to the realm of empirical vs anecdotal evidence.” There is nothing anecdotal about the systematic collection of data from a randomized