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Could conjunctivitis in dupilumab treated atopic dermatitis patients be caused by colonization with demodex and increased IL-17 levels?

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Declaration of interests

Dr. Thyssen has attended an advisory board for Roche and Sanofi-Genzyme, and been a speaker on atopic dermatitis for LEO Pharma and Sanofi-Genzyme.

Key words: Atopic dermatitis, complication, conjunctivitis, dupilumab, ocular

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To the editor,

de Bruin-Weller et al., reported alarmingly high rates of unspecified and allergic conjunctivitis in trial patients with moderate-to-severe atopic dermatitis (AD) who underwent treatment with dupilumab; an antibody that inhibits signaling of IL-4 and IL-13.¹ Importantly, the exact pathogenic mechanism behind incident conjunctivitis in dupilumab-treated patients is unclear. While all, but one case, were considered to be of mild or moderate severity, and most resolved after treatment discontinuation, ocular complications may ultimately deprive AD patients from effective treatment with dupilumab. For these reasons, the medical community needs to rapidly identify the pathogenic mechanism.

Normal facial skin is often colonized with harmless arthropods (*Demodex folliculorum* and *D. brevis*), that reside and consume sebum in the cutaneous and ocular hair follicles. Mite numbers increase with age, but are dramatically elevated in rosacea, where they may contribute to skin and ocular disease through bacteria and toxin release following death. This may in turn result in local inflammation, abnormal lipid composition of the tear film, increased evaporation from the ocular surface, dryness and conjunctivitis. Interestingly, cutaneous and ocular inflammation in rosacea seems to be IL-17 mediated.² Useful treatments include eyelid hygiene, lubrication of the ocular surface, topical cyclosporine and oral doxycycline.

Dupilumab inhibits T helper (Th) cell 2 signaling through IL-4 receptor alpha blockade, which in turn may comprise the immune response against helminth infections. It is therefore possible that demodex mites thrive in an IL-4 and IL-13 deprived cytokine milieu. Accordingly, demodex mites rapidly colonized genetically modified mice (BALB/c-IL13/IL4) with impaired Th 2 response.³ At least in theory, dupilumab treatment could increase demodex numbers in hair follicles, cause Meibomian gland dysfunction and ocular rosacea-like disease driven by IL-17 inflammation. IL-17 blocking biologicals should then theoretically benefit these patients. While it remains unknown why conjunctivitis is not a similar problem in asthmatic patients receiving dupilumab therapy, this finding

may be explained by AD being a skin condition. Thus, mites preferably colonize skin with low hydration and high pH which is often the case in AD. ⁴

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