Pilocarpine as a treatment option for dupilumab-related eye manifestations

To the Editor: The treatment of atopic dermatitis (AD) has changed dramatically after the development of dupilumab. Despite its good efficacy, AD patients frequently develop blepharoconjunctivitis after the administration of dupilumab. Dupilumab-associated ocular surface disease (DOSD) is one of the most frequently encountered side effects in clinical practice. The incidence of conjunctivitis has been reported to be 8.6 % in the CHRONOS trial and 28% in the LIBERTY AD CAFÉ trial. Although it is usually mild to moderate, it significantly affects the activities of daily living, and some patients develop severe conditions such as cicatrizing conjunctivitis.[1] Ocular manifestations can be managed with eyelid hygiene, artificial tears, antihistamine eye drops, and anti-inflammatory eye drops. However, not all cases respond well to such treatment and some patients discontinued dupilumab due to uncontrolled severe eye manifestations.[2]

We retrospectively analyzed patients who developed blepharoconjunctivitis after being treated with dupilumab. Electromedical records and photographs were reviewed, and this study was approved by the institutional review board. An ophthalmologist (Dr H.J.B.) determined the severity of conjunctivitis (none, trace, mild, moderate, or severe) based on the intensity of bulbar or palpebral hyperemia.[3] The patients' treatment response after 3 m compared to initial symptoms/signs was analyzed. Complete remission was defined as no symptoms (pain and/or itching) or signs after treatment, remission status was defined as trace conjunctivitis with 75% improved symptoms compared to baseline, stable status was defined as mild conjunctivitis with 50% improved symptoms, and worsened status was defined as moderate or severe conjunctivitis with exacerbation of subjective symptoms. In 143 patients, 31 patients (21.7%) developed ocular complications after dupilumab prescription. Three patients (9.7%) achieved complete remission after treatment, and 14 patients (45.2%) achieved remission status. Ten patients (32.3%) showed stable status compared to baseline, but 4 patients (12.9%) experienced worsening of ocular condition despite treatment (Table I). We found that a significant proportion of patients still suffered from ocular complications even after

Table I. Response to conventional treatments in dupilumab-related ocular complications

		Response to treatment			
Treatment profile	**Number of cases**	**Worsened**	**Stable**	**Remission**	**Complete remission**
Artificial tear only	1	0	0	0	1
Anti-histamine eye drop (± artificial tear)	9	0	5	4	0
Anti-inflammatory ointment* (± artificial tear & anti-histamine eye drop)	6	0	3	3	0
Anti-inflammatory eye drop† (± artificial tear & anti-histamine eye drop)	12	2	2	6	2
Anti-inflammatory ointment & anti-inflammatory eye drop (± artificial tear & anti-histamine eye drop)	3	2	0	1	0
Total	31	4 (12.9%)	10 (32.3%)	14 (45.2%)	3 (9.7%)
Sub-analysis in pilocarpine cases‡	4	0	1	1	2

*Anti-inflammatory ointment: Topical steroid or topical calcineurin inhibitor.
†Anti-inflammatory eye drop: Steroid eye drop or cyclosporine eye drop.
‡Pilocarpine 5 mg tablet was additionally prescribed to the four worsened patients who did not show response to conventional treatment, and their response to pilocarpine were categorized.

Fig 1. Dupilumab-associated blepharoconjunctivitis. Before prescribing pilocarpine (*left*), and 3 m after initiating pilocarpine (*right*).

treatment. To address this clinical problem, we tried oral pilocarpine 5 mg to the 4 worsened patients who did not experience improvement after conventional treatment, and ocular conditions were remitted in 3 out of 4 patients (Fig 1).

Several mechanisms are thought to be related with the development of DOSD, including increased demodex mites due to altered cytokine activity, increased OX40 ligand activity, eosinophilia, and decreased goblet cells.[1,2] Goblet cells are mucus-secreting cells which are important in the ocular surface barrier, and IL-13 regulates goblet cell proliferation and mucus secretion. Since dupilumab blocks the IL-13 pathway, it may lead to decreased goblet cell density and decreased mucin production, which leads to impaired ocular surface barrier and conjunctival inflammation.[4] In this regard, we thought pilocarpine, a muscarinic agonist which is known to promote the secretion of aqueous tear from conjunctiva, lacrimal glands, and mucin from goblet cells, could be considered as a treatment option for dupilumab-associated blepharoconjunctivitis.[5] Although evidence is limited due to the small number of cases, pilocarpine showed promising results in refractory blepharoconjunctivitis. Further studies are needed to clarify the exact efficacy of pilocarpine in dupilumab-associated blepharoconjunctivitis.

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Conflicts of interest

None disclosed.

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