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Recurrence of conjunctival goblet cells after discontinuation of dupilumab in a patient with dupilumab related conjunctivitis

A.N. Voorberg, MD¹; W.F.A. den Dunnen, MD, PhD²; R.H.J. Wijdh, MD³; M.S. de Bruin-Weller⁴, MD, PhD; M.L.A. Schuttelaar, MD, PhD¹

¹Department of Dermatology, University of Groningen, University Medical Center Groningen, the Netherlands.

²Department of Pathology, University of Groningen, University Medical Center Groningen, the Netherlands.

³Department of Ophthalmology, University of Groningen, University Medical Center Groningen, the Netherlands.

⁴Department of Dermatology, University Medical Center Utrecht, the Netherlands.

Corresponding author:

Marie L.A. Schuttelaar, MD, PhD

Department of Dermatology

University Medical Center Groningen

PO Box 30.001

9700 RB Groningen

The Netherlands

E-mail: m.l.a.schuttelaar@umcg.nl

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A large proportion (8.6% – 22.1%) of patients receiving dupilumab for atopic dermatitis (AD) in clinical trials develops conjunctivitis.⁽¹⁾ We describe the histopathological characteristics of a patient with a severe, new-onset conjunctivitis during dupilumab treatment and four months after discontinuation of dupilumab.

A non-atopic 36-year-old woman, without a history of asthma, rhinitis or conjunctivitis had severe AD since early childhood. She was treated with dupilumab and showed rapid efficacy; Eczema Area and Severity Index (EASI) score at week 16 was 3.9 points compared to 28.3 points at baseline.

At week 8, patient reported increasing redness and burning of the eyes. Shortly after week 16, the patient presented with moderate redness of the conjunctivae and reported itch, tearing, blurred vision, burning and foreign body sensation paired with periocular eczema and oedema. A bilateral keratoconjunctivitis was diagnosed by the ophthalmologist which was more severe with sterile corneal infiltrates in the left eye (OS). A conjunctiva biopsy was performed at the inferior bulbar conjunctiva OS and stained with haematoxylin and eosin for histological assessment and additionally with Alcian blue (mucus-containing goblet cells (GCs) and CD3/CD4/CD8 (T helper (Th) cells). Assessment showed goblet cell (GC) scarcity with a median density of 2-4 Goblet cells mm⁻¹ (*Figure 1A*) (normal GC density varies

between 8.8 and 30 cells mm⁻¹)(2), with a CD4/CD8 positive (mainly CD4 positive) T-cell infiltrate at the interface, partially migrating into the conjunctival epithelium (*Figure 1C, 1E*). Treatment with tacrolimus 0.1% ointment on the eyelids, hyaluronic acid/carbomer eye drops four times daily ODS, fluorometholone eye drops twice daily OS and one week of chloramphenicol eye drops thrice daily OS was initiated. Despite treatment the conjunctivitis and periocular eczema did not decrease in severity. Therefore, treatment with dupilumab was discontinued at 31 weeks. Subsequently, the patient was treated for her eczema with prednisolone 20mg/day for three months and azathioprine in a maintenance dose of 150mg/day. Three months later, the patient did not experience any of the previous ocular symptoms and no abnormalities were found during ophthalmologic examination. The periocular eczema resolved rapidly after discontinuation of dupilumab, but her eczema on the rest of the body and especially her hand eczema had increased in severity, despite the usage of azathioprine and prednisolone.

A follow-up conjunctival biopsy was performed at the inferior bulbar conjunctiva OD, four months after discontinuation of dupilumab. Assessment showed a normal GC density of 24-28 cells mm⁻¹ (*Figure 1B*), with significant less CD4 and CD8 positive T-cells compared to the first biopsy present in the superficial part of the conjunctival epithelium (*Figure 1D, 1F*).

In a recent study a similar remarkable scarcity of conjunctival GCs accompanied by an inflammatory T-cell infiltrate was found in patients with AD with conjunctivitis during dupilumab treatment.(3) They reported that the epithelial infiltrate consisted of multiple eosinophils in several patients, which was not the case in our patient.

This is the first case which demonstrates the recurrence of GCs with a normal density after discontinuation of dupilumab. The most likely hypothesis is blocking IL-13 by dupilumab leads to a reduction of GCs and mucin production, resulting in an irritative conjunctivitis.(3)

This case shows recovery of the GCs as soon as blocking of IL-13 and IL-4 by dupilumab is stopped. However, the treatment with prednisolone and azathioprine might have stimulated the recurrence of GCs, since several immunosuppressive drugs, such as cyclosporine and prednisolone, have been found to increase GC density.(4)

Unfortunately, no biopsy was performed before dupilumab treatment to assess if GC scarcity was already present in the patient. This is however unlikely, looking at the recurrence of GCs after discontinuation of dupilumab.

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