Long-term follow-up and treatment outcomes of conjunctivitis during dupilumab treatment in patients with moderate-to-severe atopic dermatitis

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Clinical Implications

- Ophthalmologist-confirmed conjunctivitis during dupilumab treatment was observed in 33 of 167 (19.8%) of patients with atopic dermatitis. Most patients still suffered from mild-to-moderate conjunctivitis during long-term follow-up despite treatment. Dose adjustment or discontinuation of dupilumab was needed in 10 of 33 (30%) and 3 of 33 (9%) patients, respectively.

Dupilumab is the first biologic treatment for atopic dermatitis (AD), and its effectiveness and safety are proven.[1] Although conjunctivitis is the most frequently reported side effect during dupilumab treatment in both clinical trials and daily practice, data on the clinical course of conjunctivitis during long-term use of dupilumab are lacking.[1-3] This prospective daily practice study evaluates ophthalmological characteristics and long-term treatment outcomes of ophthalmologist-confirmed conjunctivitis during dupilumab treatment in patients with moderate-to-severe AD. During a 12-month evaluation period, 167 patients with moderate-to-severe AD were treated with dupilumab 300 mg every 2 weeks, after a loading dose of 600 mg, at the University Medical Center Utrecht, the Netherlands. Patients reporting ophthalmological symptoms that could not be controlled with lubricant drops and/or tacrolimus skin ointment (1 mg/g) for the external eyelids were referred to an ophthalmologist. Further (anti-inflammatory) ophthalmological treatment was prescribed by the ophthalmologist and individually chosen per patient. Conjunctivitis was reported in 66 of 167 (39.5%) patients, of whom 33 were referred to an ophthalmologist. Ophthalmologist-confirmed conjunctivitis was reported in 33 of 167 (19.8%) patients (17 female; mean age 45.7 years, standard deviation [SD] 14.3; mean Eczema Area Severity Index at baseline, 21.7 (SD 9.5); Table E1, available in this article's Online Repository at www.jaci-inpractice.org). History of (allergic) conjunctivitis was present in 24 of 33 (72.7%) patients. None of the 33 patients reported conjunctivitis symptoms at the start of dupilumab. In the 33 referred patients, patient-reported eye symptoms, such as redness, tearing, and itching, developed within a median of 33 days (interquartile range, 28.0-61.0) after starting dupilumab. Ophthalmological characteristics were examined and graded in terms of severity by an experienced ophthalmologist following the Utrecht Ophthalmic Inflammatory and Allergic disease ocular surface score (Table I). Overall conjunctivitis severity was based on grading of different ophthalmological characteristics (Figure 1, *A* and *B*).

During the first ophthalmological consultation, mild, moderate, and severe conjunctivitis were diagnosed in 22 (66.7%), 7 (21.2%), and 4 (12.1%) of the 33 referred patients, respectively (Figure 1, *B*). Most frequently reported ophthalmological characteristics were tarsal and bulbar conjunctivitis, and blepharitis (in 28 [84.8%], 25 [75.8%], and 22 [66.7%] patients, respectively). Six (18.2%) patients presented with limbitis (Figure 1, *A*).

The most frequently prescribed ophthalmological treatments during follow-up included corticosteroid eye drops, tacrolimus skin ointment for the external eyelids, and lubricant drops (in 24 [72.7%], 25 [75.8%], and 26 [78.8%] patients, respectively; Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

During follow-up (mean, 17.5 [SD ±3.4] months), the dosing interval of dupilumab was prolonged to 300 mg every 3 to 5 weeks in 10 of 33 (30%) patients because of conjunctivitis, resulting in improvement of eye symptoms in 6 patients and remission in 1 patient. Discontinuation of dupilumab due to ocular pathology was necessary in 3 of 33 (9.1%) patients, showing improvement or remission in all cases (Figure 1, *C*). Ineffectiveness of dupilumab led to discontinuation in 2 of 33 (6.1%) patients.

After follow-up, 24 of 28 (86%) patients who continued dupilumab treatment were still suffering from conjunctivitis (Figure 1, *B*). New-onset limbitis during follow-up was seen in 8 more patients (8 of 27, 29.6%), and in 6 cases despite ophthalmic anti-inflammatory treatment.

The conjunctivitis outcome during a follow-up of 17.6 (SD ±3.5) months was evaluated for 28 of 33 (84.8%) patients who continued dupilumab, by comparing the first conjunctivitis severity category with the latest follow-up category (Figure 1, *D*). Outcomes were categorized into worsened (worsening with ≥1 category), stable (unchanged category), improved (improvement with ≥1 category), or complete remission (no conjunctivitis). Complete remission was seen in 4 of 28 (14%) patients; of these, 2 were still using anti-inflammatory eye drops or tacrolimus ointment for the external eyelids. Improvement of conjunctivitis occurred in 7 of 28 (25%) patients, of whom 6 were still using anti-inflammatory eye drops. Uncontrolled conjunctivitis, meaning stable or worsened conjunctivitis, was seen in 17 of 28 (61%) patients. Ophthalmic anti-inflammatory therapy was prescribed for all of these 17 patients; however, 2 of 17 patients reported being noncompliant.

Literature regarding conjunctivitis during dupilumab is limited by small sample sizes, short follow-up duration, and lack of thorough and standardized ophthalmological investigation. In contrast, all 33 patients of our study underwent standardized examination by an ophthalmologist followed by long-term follow-up.

Several pathomechanisms have been suggested to be responsible for the development or worsening of conjunctivitis during dupilumab treatment in patients with AD, such as rosacea-like

TABLE I. Utrecht Ophthalmic Inflammatory and Allergic disease ocular surface score

Ophthalmological characteristics	Severity*			
	None	Mild	Moderate	Severe
Blepharitis	No blepharitis	Bubbles, mild hyperemia of the eyelid	Hyperemia and mild swelling of the eyelid	Severe hyperemia, thickening, keratinization, scarring of the eyelid
Meibomian gland dysfunction	No Meibomian gland dysfunction	Bubbles, after pressing an oily substance is formed	Plugs or bubbles, after pressing an thicker substance is formed	Plugs or scarring, after pressing no substance is formed
Tarsal conjunctivitis	No tarsal conjunctivitis	Mild swelling and hyperemia, mild papillae	Larger papillae, moderate swelling and hyperemia	Moderate characteristics and/or keratinization, ulceration, sclerosis
Bulbar conjunctivitis	No bulbar conjunctivitis	Mild swelling and hyperemia	Moderate swelling and hyperemia in all quadrants	Severe swelling and hyperemia, mucus and excessive tearing, photophobia
Limbitis	No limbitis	Mild swelling and hyperemia	Evident swelling/ hyperemia over >3 clock hours	Severe swelling/hyperemia, conjunctival vascularization extending the normal limbus edge
Limbal vascularization	No abnormal limbal vascularization	Fine vascularization along the limbus	Moderate vascularization to the limbus >3 clock hours, or fine vascularization extending the normal limbus barrier	Strong vascularization extending the normal limbus barrier in >3 clock hours
Corneal punctate	No corneal punctate	Some punctate limited to the interpalpebral region	Fiddled punctate, extending the interpalpebral region or strongly present in the interpalpebral region	Significantly diffuse punctate and/or confluent
Hurricane pattern	No hurricane pattern	Elongated small and narrow punctate along the limbus to <0.25 radius and <1 clock hour	Long and thin punctate in hurricane pattern, up to <0.5 radius and <3 clock hours	Evident hurricane pattern >3 clock hours and/or 0.5 radius (cross pupil)
Overall severity of the conjunctivitis	None/mild/moderate/severe conjunctivitis†			

*None = 0 points; mild = 1 point; moderate = 2 points; severe = 3 points.
†0 = no conjunctivitis; 1-4 = mild conjunctivitis (unless the score consists of only Meibomian gland dysfunction and punctate, then the total score is 0); 5-8 = moderate conjunctivitis; ≥9 = severe conjunctivitis.

conjunctivitis, focal scarcity of intraepithelial goblet cells, and relative ocular undertreatment due to lower tissue distribution of dupilumab in the eyes.[2,4,5] The last hypothesis seems in contradiction with our finding that interval prolongation or discontinuation of dupilumab resulted in improvement of the conjunctivitis.

The management of conjunctivitis during dupilumab treatment is challenging. Previous case series and case reports have described several therapeutic options, including tacrolimus eye ointment, fluorometholone eye drops, cyclosporine eye drops, and lifitegrast eye drops, leading to improvement in most cases.[6-8] The majority of our patients received combination therapy, and most patients remained dependent on ophthalmic medication. Anti-inflammatory eye drops and/or tacrolimus ointment for the external eyelids were prescribed most often.

In contrast to clinical trial data, reporting that most conjunctivitis cases recovered or resolved while continuing dupilumab treatment, our results show more persistent ophthalmological signs and symptoms despite adequate ophthalmic treatment. Remarkably, 8 of 33 (24.2%) patients developed limbitis during follow-up, and 6 cases despite adequate ophthalmic anti-inflammatory treatment. Limbal stem cells are vital for corneal healing and the barrier function of the limbus. Chronic limbitis may lead to irreversible limbal stem cell deficiency, which could lead to irreversible long-term visual loss, making adequate monitoring of conjunctivitis necessary.[9]

This study has some limitations. First, because all patients were seen in an AD expertise center, the population consisted of patients with more severe AD. As severity of AD may be related to the development of conjunctivitis during dupilumab

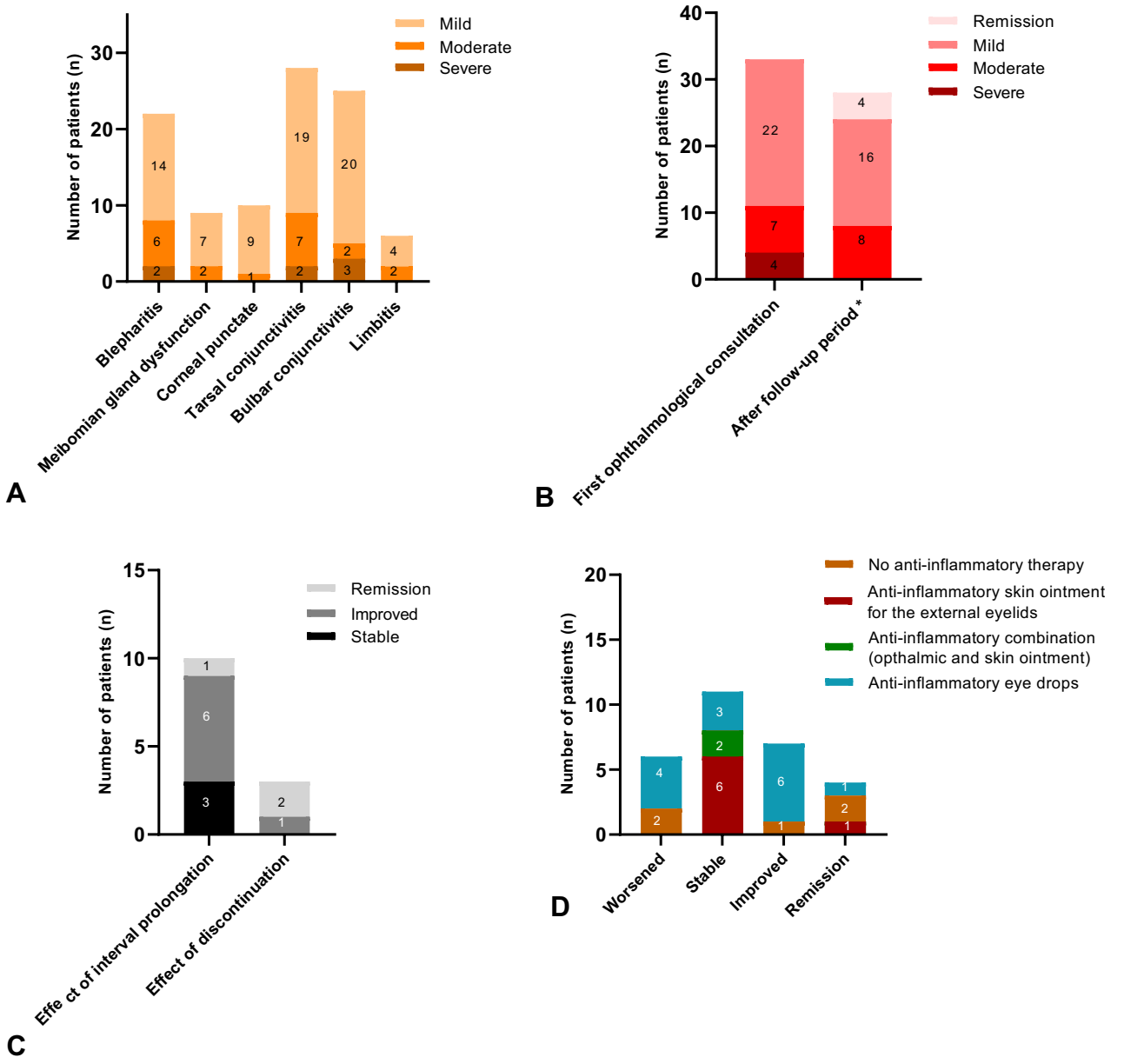

FIGURE 1. Results of 33 patients with atopic dermatitis diagnosed with conjunctivitis during dupilumab treatment. **A,** Ophthalmic characteristics at the first ophthalmological consultation (n = 33). **B,** Severity of conjunctivitis at the first consultation (n = 33) and after follow-up (n = 28). **C,** Effect of dose adjustment of dupilumab due to ocular pathology. **D,** Outcome and treatment of conjunctivitis after follow-up (n = 28). *Discontinued patients (n = 5) were excluded.

treatment, this may have affected the results.[2] Secondly, not all patients may have been compliant with ophthalmic treatment, which might have resulted in undertreatment of the conjunctivitis. Lastly, ophthalmological examination by an ophthalmologist was not performed before starting dupilumab; therefore, pre-existing ophthalmological pathology cannot be excluded.

In conclusion, this study shows ophthalmologist-confirmed conjunctivitis in 33 of 167 (19.8%) patients with AD treated with dupilumab in a 1-year period. During long-term ophthalmological follow-up, the majority of these patients still suffered from mild-to-moderate conjunctivitis despite treatment. Dose adjustment or discontinuation of dupilumab due to ocular pathology was needed in 10 of 33 and 3 of 33 of the patients, respectively.

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Conflicts of interest: D. Bakker, J. Thijs, J. van der Schaft, and C. van Luijk are speakers for Sanofi Genzyme. J. de Boer received research funding from Abbvie; this is outside the submitted work. D. Balak is a speaker and/or advisor for AbbVie, Leo Pharma, Regeneron, and Sanofi-Genzyme. M. de Graaf is a principal investigator and advisory board member for Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.; and is an advisory board member for Eli Lilly. M. de Bruin-Weller is a principal investigator, advisory board member, and consultant for AbbVie, Regeneron Pharmaceuticals Sanofi-Genzyme, and Leo Pharma; is an advisory board member and consultant for Eli Lilly, UCB, and Galderma; and is a principal investigator and advisory board member for Pfizer. The rest of the authors declare that they have no relevant conflicts of interest.

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TABLE E1. Baseline table

	Total group (n = 33)
Sex, female, n (%)	17 (51.5)
Age (y) at the start of dupilumab, mean (SD)	45.7 (14.3)
Age of primary onset AD	
Childhood, n (%)	28 (84.8)
Adolescence, n (%)	4 (12.1)
Adult, n (%)	1 (3.0)
No. of prior immunosuppressive systemic treatments for AD (used for at least 3 mo), median (IQR)	2.0 (1.0-4.0)
Hospitalized for AD ever, n (%)	27 (81.8)
Atopic comorbidities	29 (87.9)
Allergic asthma, n (%)	23 (69.7)
Allergic rhinitis, n (%)	23 (69.7)
Allergic conjunctivitis, n (%)	24 (72.7)
Food allergy, n (%)	21 (63.6)
AD related parameters at the start of dupilumab	
EASI score baseline, mean (SD)	21.7 (9.5)
TARC (pg/mL), median (IQR)	2856 (1271-8000)
Eosinophils ($\times 10^9$/L), median (IQR)	0.38 (0.26-0.72)
AD-related parameters at referral to the ophthalmologist	
EASI score, mean (SD)	8.0 (5.8)
TARC (pg/mL), median (IQR)	625 (413-938)
Eosinophils ($\times 10^9$/L), median (IQR)	0.62 (0.30-1.30)
No. of days between the start of dupilumab and development of eye symptoms, median (IQR)	33.0 (28.0-61.0)
No. of days between the start of dupilumab and referral to the ophthalmologist, median (IQR)	94.0 (54.5-147.5)
No. of ophthalmological consultations, median (IQR)	4.0 (2.5-8.0)
Total follow-up period (both dermatological and ophthalmological) (mo), median (IQR)	22.0 (18.0-24.0)
Follow-up period since ophthalmological baseline(mo), mean (SD)	17.5 (3.4)
History of ocular disease (excluding allergic conjunctivitis)	11 (33.3)
History of atopic keratoconjunctivitis, n (%)	5 (45.5)
Active conjunctivitis at the start of dupilumab, n (%)	0 (0.0)
Rosacea	
History of rosacea, n (%)	4 (12.1)
Rosacea flare during follow-up, n (%)	6 (18.2)
Development of head-neck dermatitis during follow-up, n (%)	2 (6.1)

Data are n (%) unless otherwise indicated. Childhood is <12 years, adolescence is 12-17 years old, and adult is >18 years old.
AD, Atopic dermatitis; *EASI*, Eczema Area Severity Index; *IQR*, interquartile range; *SD*, standard deviation; *TARC*, thymus- and activation-regulated chemokine.

TABLE E2. Treatment for conjunctivitis, number of total prescribed treatments during follow-up

Prescribed therapies as treatment for conjunctivitis during follow-up	n = 33
Lubricant drops	26 (78.8)
Anti-inflammatory therapy for the external eyelids	25 (75.8)
Antihistamine eye drops	14 (42.4)
Corticosteroid eye drops	24 (72.7)
Other anti-inflammatory therapy (eye drops/eye ointment)	12 (36.4)
Combined anti-inflammatory and antimicrobial therapy (eye drops/eye ointment)	10 (30.3)
Other therapy	3 (9.1)

Data are n (%) unless otherwise indicated. Multiple therapies per patient.
Anti-inflammatory treatment for the external eyelids included tacrolimus skin ointment; corticosteroid eye drops included fluorometholone, dexamethasone, hydrocortisone, softacor, and prednisolone; antihistamine eye drops included ketotifen; other anti-inflammatory therapy (eye drops/eye ointment) included tacrolimus eye ointment and cyclosporine A eye drops; combined anti-inflammatory and antimicrobial treatment (eye drops/eye ointment) is terracortril and tobradex; other therapies are cross-linking, and bandage lens with chloramphenicol.