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

Rosie Achten, MD, PhD*, Daphne Bakker, MD, PhD*, Lieneke Ariens, MD, PhD, Amanda Lans, MD, PhD, Judith Thijs, MD, PhD, Jorien van der Schaft, MD, PhD, Joke de Boer, MD, PhD, Deepak Balak, MD, PhD, Marlies de Graaf, MD, PhD, Chantal van Luijk, MD, PhD, and Marjolein de Bruin-Weller, MD, PhD

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. 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. 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 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, A). 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
conjunctivitis, focal scarcity of intraepithelial goblet cells, and relative ocular undertreatment due to lower tissue distribution of dupilumab in the eyes. 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. 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.

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

| TABLE I. Utrecht Ophthalmic Inflammatory and Allergic disease ocular surface score |
|---------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Ophthalmological characteristics | None                          | Mild                          | Severe                        |
| Blepharitis                      | No blepharitis                | Bubbles, mild hyperemia 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 |
| Tarsal conjunctivitis            | No tarsal conjunctivitis      | Mild swelling and hyperemia, mild papillae | Larger papillae, moderate swelling and hyperemia |
| Bulbar conjunctivitis            | No bulbar conjunctivitis      | Mild 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 |
| 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 |
| 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 |
| 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 |
| Overall severity of the conjunctivitis | None/mild/moderate/severe conjunctivitis | Significantly diffuse punctate and/or confluent |

*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.
treatment, this may have affected the results. 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.

Acknowledgment

We would like to thank Andrew Walker for critically reading the manuscript.

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.

A

B

C

D
These authors contributed equally to this work.

Patients included in this manuscript participated in the BioDay registry sponsored by Sanofi Genzyme.

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; and 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.

Received for publication June 24, 2020; revised August 6, 2020; accepted for publication September 17, 2020.

Available online October 7, 2020.

Corresponding author: Roselie Achten, MD, Department of Dermatology and Allergology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands. E-mail: R.E.Achten@umcutrecht.nl.

© 2020 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

https://doi.org/10.1016/j.jaip.2020.09.042

REFERENCES

1. de Bruin-Weller M, Thaci D, Smith CH, Reich K, Cork MJ, Radin A, et al. Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). Br J Dermatol 2018;178:1083-101.

2. Akinlade B, Gottman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol 2019;181:459-73.

3. Ariens LFM, van der Schaft J, Bakker DS, Balak D, Romeijn MLE, Kouwenhoven T, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: first clinical and biomarker results from the BioDay registry. Allergy 2020;75:116-26.

4. Bakker DS, Ariens LFM, van Luijc C, van der Schaft J, Thijs JL, Schuttelaar MLA, et al. Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis. Br J Dermatol 2019;180:1248-9.

5. Simpson EL, Akinlade B, Ardeleanu M. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2017;376:1090-1.

6. Wollenberg A, Ariens L, Thurau S, van Luijc C, Seegraber M, de Bruin-Weller M. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab-clinical characteristics and treatment. J Allergy Clin Immunol Pract 2018;6:1778-17780.e1.

7. Roca-Gines J, Rahhal-Ortuno M, Torres-Navarro I, Rodriguez-Serna M, Navarro-Mira MA. Cyclosporine 0.1% (Ikervis®) treatment in steroid-dependent dupilumab-associated conjunctivitis. Arch Soc Esp Oftalmol 2019;94:396-4.

8. Zirwas MJ, Wulff K, Beckman K. Lifitegrast add-on treatment for dupilumab-induced ocular surface disease (DIOSD): a novel case report. JAAD Case Rep 2019;5:34-6.

9. Puangsricharern V, Tseng SC. Cytologic evidence of corneal diseases with limbal stem cell deficiency. Ophthalmology 1995;102:1476-85.
# 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 (×10⁹/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 (×10⁹/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.