

Letter regarding “Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab—clinical characteristics and treatment”



To the Editor:

A recent report by Wollenberg et al¹ described that up to 50% of patients with moderate to severe atopic dermatitis (AD) treated with dupilumab developed severe conjunctivitis, which was more likely to develop in patients with more severe AD baseline as described recently.² The severity of conjunctivitis was so severe as to stop treatment with dupilumab in some patients.¹ The most characteristic features found were inflammation of the anterior conjunctiva and hyperemia of the limbus being treated with fluorometholone or tacrolimus.¹ Nevertheless, a causal relationship has not been well established. During the clinical development of dupilumab in AD,³ the incidence of conjunctivitis was around 10% and infrequent in patients with asthma or nasal polyposis, suggesting that some characteristics of patients with AD may contribute to its cause, as can be eye involvement as a comorbidity of AD.

The cause of conjunctivitis in patients with AD is not yet fully understood, but it seems that IL-13 is involved in regulating conjunctival goblet cells and therefore the quality of the tear.³⁻⁵

In this article, we report our experience with this adverse effect. Ten patients with severe AD have undergone an ophthalmological evaluation at 12 weeks of treatment with dupilumab. The assessment was carried out by an ophthalmologist, and all patients were assessed by slit lamp and corneal exploration after Colircusi Fluotest (Alcon, El Masnou, Spain) staining. All patients treated with dupilumab in this number of cases suffered from severe AD (SCORing Atopic Dermatitis score > 40; average, 65.4; Eczema Area and Severity Index > 22; average, 22.8). Treatment with dupilumab was initiated because of a lack of clinical response with immunosuppressants. Only 1 of our patients had a history of ophthalmological pathology (glaucoma and keratitis), not referring to any other ocular discomfort before treatment. In all patients we prescribed a treatment with artificial tears (Artelac Complete, Bausch & Lomb, Bridgewater, NJ) every 12 hours from 1 week before starting treatment with dupilumab. Clinical improvement in dermatitis began to be seen after week 4, and none of the patients reported ocular discomfort at that time. Twelve weeks after beginning treatment with dupilumab, all the patients were evaluated by an ophthalmologist. In only 1 patient a superficial punctate keratitis was observed (prevalence of 10%), which was the one who had already suffered ophthalmological problems in the past. In our case series, the incidence of conjunctivitis was lower than that described by Wollenberg et al,¹ being similar to that described in the precommercial development studies of dupilumab.³

In conclusion, we believe that recommending artificial tears to patients with AD treated with dupilumab can reduce the incidence of conjunctivitis and keratitis.

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Conflicts of interest: J. Sastre reports having served as a consultant to Thermofisher, Novartis, Sanofi, Leti, Faes Farma, Mundipharma, and GlaxoSmithKline; having been paid lecture fees by Novartis, GlaxoSmithKline, Stallergenes, LETI, and Faes Farma; and having received grant support for research from Thermofisher and ALK. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication September 22, 2018; accepted for publication October 3, 2018.

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<https://doi.org/10.1016/j.jaip.2018.10.055>

Reply



To the Editor:

Rial et al¹ communicate their experience of an unspecified artificial tear preparation 1 week before starting dupilumab treatment (as a preventive treatment), which they have quite successfully used in 10 patients with dupilumab-associated conjunctivitis. We see this report of their experience as a valuable addition to our published report on this reaction pattern,² which is associated with the use of dupilumab in patients with atopic dermatitis, but not with its use in other indications such as polyposis nasi, allergic asthma, or eosinophilic esophagitis. The reported incidence in clinical trials is between 5% and 28% of dupilumab-treated patients.¹

It would be valuable to the larger scientific community to learn about the long-term results with this treatment option as a preventive strategy. It is important to realize that artificial tears do not replace the mucus that is produced by the goblet cells. Hence, artificial tears may be a preventive strategy to possibly prevent some degree of irritative conjunctivitis due to decreased mucus production, but will not target the assumed original problem of decreased mucus production.

Because the compounding of the tacrolimus eye ointment may not be possible in some countries, we want to draw the attention to another anti-inflammatory treatment option without risk for glaucoma or cataract. Oily ciclosporin 1% eye drops NRF 15.21. may be compounded following the German compounding standard of the Nationales Rezeptur Formularium.³

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Conflicts of interest: A. Wollenberg reports consultancy arrangements with Almirall, Anacor, Galderma, Hans Karrer, MedImmune, Pfizer, Pierre Fabre, Regeneron, and Sanofi; research grants from Beiersdorf and LEO; and honoraria for lectures from Almirall, Bioderma, Chugai, Galderma, LEO, L'Oreal, Maruho, MedImmune, Novartis, Pfizer, Pierre Fabre, Regeneron, and Sanofi, all outside the submitted work. M. de Bruin-Weller reports consultancy arrangements with Abbvie, Regeneron, and Sanofi and grants from Abbvie, Regeneron, and Sanofi, all outside the submitted work. S. Thureau declares no relevant conflicts of interest.

Received for publication October 26, 2018; accepted for publication October 27, 2018.

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<https://doi.org/10.1016/j.jaip.2018.10.054>

C1-INH concentrate for prophylaxis during pregnancy in hereditary angioedema with normal C1-INH



In the *Journal of Allergy and Clinical Immunology: In Practice* article "Use of pdC1-INH concentrate for long-term prophylaxis during pregnancy in hereditary angioedema with normal C1-INH," Garcia et al¹ proposed a study for long-term prophylaxis of hereditary angioedema (HAE) with normal C1-INH in pregnancy. Although it was regarded as the first study for such a protocol, a similar article "Successful perinatal management of hereditary angioedema with normal C1 esterase inhibitor and factor XII mutation using C1 esterase inhibitor therapy" by Gibbons et al² was published in print 6 months earlier in the journal *Annals of Allergy, Asthma, and Immunology* on December 2017. Our publication was available online and 3 days after the listed initial submission to *JACI: In Practice* by Garcia et al. These unique cases resemble the action of 2 ships unknowingly passing each other on a moonless night.

Although both articles display a systematic way to provide plasma-derived C1-INH, their dosage and frequency vastly differ. Garcia et al followed 3 cases of type III HAE and proposed a dose of 1000 International Units (IU) once or twice a week, which greatly reduced the frequency of attacks from once or twice a week to none or once a month. In contrast, the article by Gibbons et al offered a differing dose and frequency for plasma-derived C1-INH. They reported a case in a pregnant woman who had angioedema attacks starting at 16 weeks of pregnancy occurring at a frequency of up to 3 attacks a week. The authors suggested infusions every 3 days. After starting the patient on 1500 IU of

plasma-derived C1-INH prophylactic infusion every 3 days at 24-week gestation, the patient only experienced 4 additional episodes requiring rescue doses of C1-INH.

Both articles describe similar genetics involving mutation of coagulation factor XII along with the possibility of estrogen-mediated angioedema with normal C1-INH quantity and function. The treatment dosage and frequency slightly differ in each article; however, they both demonstrate the value of life-saving plasma-derived C1-INH to reduce or eliminate the threat of angioedema in pregnancy. These articles exemplify the importance of establishing a life-saving protocol for those with type III HAE.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest. Received for publication October 1, 2018; Revised October 13, 2018; accepted for publication October 16, 2018.

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<https://doi.org/10.1016/j.jaip.2018.10.056>

Reply



To the Editor:

Hereditary angioedema (HAE) is clinically characterized by recurrent cutaneous and mucosa angioedema induced by over-concentration of bradykinin in tissues. HAE is associated with high morbidity and mortality, because patients have disabling angioedema attacks, usually inadvertently undergo exploratory laparotomy as a result of abdominal angioedema, and live with the risk of having laryngeal angioedema that can lead to death due to asphyxia. Therefore, proper management of these patients is essential to improve their quality of life and minimize the risks.¹

Pharmacotherapy of HAE is divided into 3 modalities: long-term prophylaxis, short-term prophylaxis, and treatment of acute attacks. The objective of long-term prophylaxis in HAE is to reduce the frequency and severity of attacks, and it should be personalized based on 4 variables: frequency and severity of HAE attacks, impact of these attacks on the patient's quality of life, and availability of treatment for HAE attacks. Worldwide, 3 treatment modalities for long-term prophylaxis have been used: attenuated