

Dupilumab-induced ocular surface disease (DIOSD) in patients with atopic dermatitis: clinical presentation, risk factors for development and outcomes of treatment with tacrolimus ointment

Yoav Nahum,^{1,2} Michael Mimouni,^{3,4} Eitan Livny,^{1,2} Irit Bahar,^{1,2} Emmilia Hodak,^{2,5} Yael Anne Leshem^{2,5}

¹Ophthalmology, Rabin Medical Center, Petah Tikva, Israel

²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

³Ophthalmology, Rambam Health Care Campus, Haifa, Israel

⁴Technion Israel Institute of Technology Ruth and Bruce Rappaport Faculty of Medicine, Haifa, Israel

⁵Dermatology, Rabin Medical Center, Petah Tikva, Israel

Correspondence to

Dr Yoav Nahum, Ophthalmology, Rabin Medical Center, Petah Tikva, Israel; yoav.nahum@gmail.com

Received 30 July 2019

Revised 6 September 2019

Accepted 13 September 2019

ABSTRACT

Aim To identify risk factors for the development of dupilumab-induced ocular surface disease (DIOSD) in adult patients with atopic dermatitis (AD) and describe outcomes of treatment.

Methods A retrospective institutional cohort study performed at the Rabin Medical Center, Petah Tikva, Israel. Adult patients with AD who received dupilumab from March 2018 to June 2019 were included. Demographics, AD severity scores, blood IgE levels, previous atopic keratoconjunctivitis (AKC), dermatological response to dupilumab, ophthalmological evaluation and treatment were noted. Univariate and multivariate analyses were used to identify risk factors for DIOSD.

Results Sixteen of 37 patients who were included in the study (43%) had new or exacerbated symptoms of ocular surface disease starting at 2 weeks following the first treatment. Three patients reported transient dry eye sensation which lasted 2 weeks; nine patients reported chronic dry eye sensation, and four patients (25%) had marked blepharoconjunctivitis. The presence of severe AD was the strongest predictor of DIOSD. Not a single patient with moderate AD had DIOSD. In multivariate analysis, prior AKC was a risk factor for DIOSD ($R^2=15.78$, $OR=23.28$, $p=0.005$) while a family history of atopy was protective of DIOSD ($R^2=6.22$, $OR=0.13$, $p=0.05$). All four patients with blepharoconjunctivitis had resolution of signs, and symptoms within days of starting periocular 0.03%–0.1% tacrolimus ointment.

Conclusions DIOSD is common in patients with AD receiving dupilumab. While most cases are mild, some patients can develop blepharoconjunctivitis which responds well to tacrolimus ointment. AD severity, and previous AKC are risk factors for DIOSD.

INTRODUCTION

Atopic dermatitis (AD) is a chronic disease characterised by robust type 2 helper T cell (Th2)-mediated immune responses to environmental antigens, refractory pruritus and susceptibility to skin infection.¹ AD is common, with a prevalence between 2%–10% in adults and 15%–30% in children. Ocular surface diseases, such as allergic conjunctivitis, blepharitis and keratitis, are well-known ophthalmic complications in patients with severe AD (termed atopic keratoconjunctivitis (AKC)), with incidence rates

of 32%–56%.^{1–2} Dupilumab is a human monoclonal antibody that blocks interleukin (IL)-4, and IL-13 signalling. It is the first US Food and Drug Administration-approved drug for the treatment of moderate-to-severe AD in patients aged >12 years inadequately controlled with topical prescription therapies. In the European Union, it is approved for use in adults with inadequately controlled, moderate-to-severe AD who are candidates for systemic therapy.³ In Israel, dupilumab was approved on December 2018 and introduced to the Israeli Health basket (ie, became available to all Israeli citizens) for adult patients with moderate-to-severe AD who failed at least two systemic treatments for AD, including phototherapy, ciclosporin, methotrexate, azathioprine and mycophenolate mofetil. On January 2019, this requirement was revised to reflect a failure of a single systemic agent, excluding phototherapy. Ocular surface disease is the most common side effect reported for dupilumab in AD (termed in one paper dupilumab-induced ocular surface disease (DIOSD)).^{1–4} Reported clinical presentations of DIOSD include self-limiting conjunctivitis, blepharoconjunctivitis, cicatricial ectropion, follicular conjunctivitis, keratitis, eye pruritus and dry eye occurring commonly from 2 to 44 weeks after initiating dupilumab treatment.^{1,3,5,6} DIOSD occurred in up to 22% of patients with AD in randomised controlled trials (RCTs),^{7,8} and in up to 50% in case series.^{3,9} Interestingly, higher prevalence of ocular surface disease was not reported for patients receiving dupilumab for the treatment of asthma, chronic rhinosinusitis with nasal polyps and eosinophilic oesophagitis.³ Treatments for this condition include artificial tears, corticosteroid drops, antihistamines or mast cell stabilisers and topical tacrolimus, a macrolide calcineurin inhibitor.^{3,9} A meta-analysis of RCTs reported several risk factors for DIOSD including increased AD severity, self-reported previous conjunctivitis and higher blood levels of IgE, and eosinophils.³ The aim of this study was to describe the characteristics of DIOSD, and to ascertain previously identified risk factors in a real-life setting of a university hospital in Israel.

METHODS

This was a retrospective cohort institutional study conducted at the dermatology and ophthalmology outpatient clinics of Rabin Medical Center, a university hospital.



© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Nahum Y, Mimouni M, Livny E, et al. *Br J Ophthalmol* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bjophthalmol-2019-315010

The cohort comprised all consecutive adult patients (aged >18 years) with AD who received dupilumab (Dupixent, Sanofi and Regeneron Pharmaceuticals, New Jersey, USA) from March 2018 (when dupilumab became available in Israel) to June 2019 at the Rabin Medical Center with at least 3 months of follow-up. All participants were followed up at an AD clinic and examined by an AD specialist (YAL).

Demographic details, baseline AD severity score, applying an Investigator Global Assessment (IGA) scale of 0–5 (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe, 5=very severe), blood IgE levels, self-reported previous AKC, dermatological response to dupilumab, ophthalmological evaluation and treatment were noted and the group of patients that developed DIOSED was compared with the group of patients that did not.

We defined presumed DIOSED as any new or exacerbated symptoms (pain, foreign body sensation, pruritus, etc) or signs (blepharitis, conjunctivitis) of ocular surface disease following dupilumab. We defined positive dermatological response to dupilumab as post-treatment IGA score ≤ 2 and a drop of at least 2 IGA points (eg, from 4 to 2, or from 3 to 1).

Statistical analysis

Data were analysed with the Minitab Software, V.17 (Minitab, State College, Pennsylvania, USA). For the analysis of continuous data, Student's *t*-tests were used for normally distributed variables and Kruskal-Wallis for non-parametric variables. For the analysis of categorical variables, χ^2 or Fishers' exact tests were used and when applicable, OR values were calculated. Finally, a binary logistic regression analysis was performed in an attempt to determine predictors for DIOSED. For this purpose, independent variables that reached a significance level of <0.10 in univariate analysis were included. In all analyses, a two-sided *p* value <0.05 was considered to be statistically significant. All presented means are accompanied by their respective SD.

RESULTS

The study cohort included 37 patients aged 46.4 ± 20.7 years (18–84 years) with 64.8% being of male gender (24 males and 13 females). Five additional patients were excluded because of insufficient follow-up. The mean follow-up time was 10.5 ± 2.9 months (5–15 months).

DIOSED developed in 43.2% (*n*=16) of the patients, starting at 2 weeks and up to 4 months following the first treatment. All patients with presumed DIOSED were examined by a cornea and external eye disease specialist (YN). Three patients reported transient dry eye sensation which lasted 2 weeks. Nine patients reported chronic dry eye sensation. In these patients, findings included minimal or no inferior punctate corneal fluorescein staining, and most patients had mild Meibomian gland disease. Anaesthetised Schirmer test was performed in five of these patients and was abnormal (3–4 mm) in two of them.

Four patients (4/16, 25%) had marked blepharoconjunctivitis and suffered from severe ocular pruritus, and irritation. In these patients, findings included periocular eczema, Meibomian gland disease, thickening and hyperaemia of lid margin to the point of mechanical ectropion (figure 1). The bulbar conjunctiva was hyperaemic, and corneas were noted for mild punctate fluorescein staining.

Of the patients who reported previous AKC, all but two had only mild papillary reaction and hyperaemia of the superior pretarsal conjunctiva, no giant papillae and no corneal findings. Two patients had corneal scarring from previous herpetic infections and subepithelial scarring of the superior pretarsal

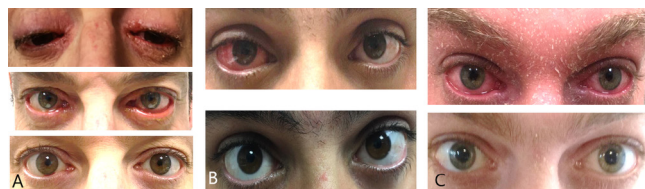


Figure 1 (A) A man aged 46 years, 6 weeks after starting dupilumab. Marked periocular eczema and blepharoconjunctivitis can be seen (top, middle). The same patient 3 weeks after starting periocular tacrolimus ointment twice daily (bottom). (B) A man aged 24 years, 4 months after starting dupilumab. The patient presented with bulbar conjunctivitis (top). The same patient 3 weeks after starting periocular tacrolimus treatment (bottom). (C) A man aged 27 years, 2 months after starting dupilumab treatment (top). The same patient 2 months after starting tacrolimus ointment treatment (bottom).

conjunctiva. Most of these patients reported using lubricating drops occasionally, and one of them reported using short courses of steroid drops in the past.

Risk factors for DIOSED

Table 1 depicts a comparison between the DIOSED group and the control group.

In terms of IGA scores, there were no cases of a score of 3 in the DIOSED group while patients with IGA score of 5 were significantly more common in the DIOSED group (75% vs 17.6%, *p*=0.001). The DIOSED group had a greater proportion of patients with prior AKC (87.5% vs 23.5%, *p*=0.001). Dermatological response to treatment was not predictive of DIOSED. Results were similar for this factor also when we used a more strict definition of achieving IGA score of 1 or 0 (*p*=0.96).

Table 2 depicts the results of the binary logistic regression analysis including all factors that were *p*<0.1 in univariate analysis. IGA score of 3 was not included as a factor as it was a perfect predictor, that is, there were no cases of DIOSED in patients with moderate AD (IGA=3). All cases of DIOSED had IGA scores of 4 or 5.

Briefly, a family history of AD was protective of DIOSED ($R^2=6.22\%$, OR=0.13, *p*=0.05) while prior AKC was a risk factor for DIOSED ($R^2=15.78\%$, OR=23.28, *p*=0.005). Every single patient without a family history of AD but a history positive for prior AKC developed DIOSED (specificity 100%, sensitivity 56.25%, positive predictive value 100%, negative predictive value 75%).

Outcomes of treatment

Patients with chronic dry eye sensation received preservative-free lubrication drops. When accompanied by eye pruritus, patients received also olopatadine or azelastine, antiallergic drops with H1 antihistaminic and mast cell stabilising properties, given twice daily. Under this treatment, all patients experienced alleviation of symptoms and no patient required corticosteroid or other treatment.

Patients with blepharoconjunctivitis were treated also with 0.03% or 0.1% tacrolimus ointment (Protopic, Leo Pharma, New Jersey, USA) applied to the skin of the eyelids twice daily for 3 weeks and then tapered down gradually to twice a week. All four patients with blepharoconjunctivitis had rapid resolution of signs and symptoms within days of initiating tacrolimus ointment (figure 1).

Table 1 Univariate analysis comparing patients with atopic dermatitis with DIOSD with patients with atopic dermatitis who received dupilumab but did not develop ocular surface disease

Parameter	DIOSD (n=16)	No DIOSD (n=21)	OR (95% CI)	P value*
Gender (% male)	75	57.1	2.25 (0.54 to 9.35)	0.26
Age (years)	41.3±17.3	50.3±22.6	0.98 (0.95 to 1.01)	0.18
Childhood onset (%)	68.7	42.9	2.93 (0.75 to 11.49)	0.12
Family history of atopy (%)	37.5	66.7	0.30 (0.08 to 1.17)	0.08
Concurrent allergic rhinitis (%)	62.5	47.6	1.83 (0.49 to 6.90)	0.37
Concurrent asthma (%)	43.7	28.6	1.94 (0.50 to 7.64)	0.34
IgE levels (UI/mL)	15692±14 862	8549±14 029	1.04 (0.99 to 1.09) for 1000 increment	0.16
IGA score				
3	0%	42.2%	N/A	<0.001
4	25%	40.2%	0.48 (0.11 to 2.11)	0.33
5	75%	17.6%	14 (2.60 to 75.41)	0.001
Prior AKC	87.5%	23.5%	22.75 (3.55 to 145.80)	<0.001
Positive dermatological response to dupilumab	68.7%	57.1%	1.65 (0.42 to 6.46)	0.74

AKC, atopic keratoconjunctivitis; DIOSD, dupilumab-induced ocular surface disease; IGA, Investigator Global Assessment; N/A, not available.

DISCUSSION

Prevalence, timing and clinical presentation patterns of DIOSD in our cohort of patients with AD treated with dupilumab are compatible with the existing literature.^{3,9} DIOSD is a common adverse event of dupilumab treatment, with 43% of patients in our cohort depicting some form of the disease. While most patients presented with mild ocular surface irritation, 11% of patients developed significant blepharoconjunctivitis. This side effect caused considerable discomfort to these patients, to the point of considering the discontinuation of a drug that alleviated their chronic debilitating skin disease following years of other unsuccessful treatment attempts. Rapid diagnosis and treatment of DIOSD enabled these patients to continue to enjoy the benefits of this drug. This was possible due to a close collaboration between dermatologists and ophthalmologists in our institution, awareness of this complication and regular follow-up of patients receiving dupilumab. Some patients were seen in our ophthalmology clinics only after weeks of being misdiagnosed, undertreated and even advised to discontinue dupilumab. Recommending dupilumab discontinuation these cases contrasts with a recent consensus recommendation by an international panel of eczema experts, stating that dupilumab treatment should be continued when possible for patients with AD and ocular complications, with appropriate referral to an ophthalmologist.¹⁰ Therefore, familiarity of ophthalmologists with this condition and its treatment is key.

The aetiology of DIOSD is not clearly understood. Proposed mechanisms included scarcity of conjunctival goblet cells,¹¹ and

demodex colonisation¹² but these are not compatible with the transient nature of most DIOSD cases. The rapid response to tacrolimus ointment seen in this study points towards an aetiology of immune dysregulation. Preferential involvement of the inferior lid margin to the point of mechanical ectropion, as can be seen in figure 1, may suggest that the inciting factor exists in the patients' tears, and further research may elucidate that hypothesis.

Recently, a meta-analysis of RCTs showed that previously reported conjunctivitis and increased AD severity were associated with increased rate of DIOSD.³ Our study supports these findings, and shows that indeed these are independent risk factors for the development of this condition.

The same study suggested that positive dermatological response to dupilumab is a protective factor for DIOSD.³ We found no such association. Conversely, all four patients who had the most severe DIOSD had positive dermatological response to dupilumab.

Family history of atopic diseases (asthma, allergic rhinitis, allergic conjunctivitis and AD) is a well-established risk factor for the development of AD. Approximately 70% of patients with AD have a positive family history of atopic diseases.¹³ In our cohort, 20/37 (54%) of patients had a family history of atopic diseases, and this was a protective factor in multivariate analyses as described in the 'Results' section. We currently have no explanation for this unexpected observation. It is possible that patients had recall limitations when eliciting a family history, especially regarding parental history in cases of elderly patients, leading to some misclassification.

Previous reports have described patients with severe DIOSD as having 'cicatrising conjunctivitis' or 'cicatricial ectropion'.^{2,5} No patient in our study had any conjunctival cicatrix (ie, symblephara, subepithelial fibrosis or fornix foreshortening) and following treatment, all conjunctiva appeared normal. Also, in all cases presenting with ectropion there was total resolution of the ectropion following therapy (figure 1), which suggests that the ectropion in these cases is mechanical and not cicatricial. A cicatricial ectropion is caused by shortening of the lid skin and would probably remain following treatment.

In their study of 13 patients with DIOSD, Wollenberg *et al* reported that while antihistamine eye drops and artificial tears did not confer any alleviation for DIOSD, topical steroids and 0.03% tacrolimus ointment resulted in improvement or complete

Table 2 Multivariate analysis depicting factors associated with DIOSD

Parameter	R ²	OR (95% CI)	P value*
Family history of atopy	6.22%	0.13 (0.01 to 1.34)	0.05
Prior AKC	15.78%	23.28 (1.81 to 299.51)	0.005
†Moderate AD (IGA=3)	N/A	N/A	N/A
Very severe AD (IGA=5)	21.69%	2.94 (0.38 to 22.55)	0.31

*All variables p<0.10 in univariate analysis were included in a binary logistic regression analysis. Performing the binary logistic regression with factors that were p<0.15 or p<0.30 in univariate analysis led to similar findings.

†IGA score of 3 were not included as this was a perfect predictor.

AKC, atopic keratoconjunctivitis; DIOSD, dupilumab-induced ocular surface disease; IGA, Investigator Global Assessment; N/A, not available.

resolution of signs and symptoms in all patients.⁹ In cases where DIOSD presented as new or exacerbated dry eye sensation with no signs of conjunctivitis, blepharitis or periocular eczema, we found that artificial tears and combined antihistamine-mast cell stabiliser drops were a sufficient treatment. Although none of these patients had shown signs compatible with AKC activity (eg, upper pretarsal conjunctival oedema, giant papillae), it might be that their symptoms resulted at least partially from exacerbation of mechanisms related to AKC that in their mildest forms are known to respond to these medications.

We try to avoid corticosteroid drops in patients with AD because of their well-known propensity for herpetic eye disease.¹⁴ Also, in one of our patients, a prolonged trial of topical steroid had no effect on severe blepharoconjunctivitis. Tacrolimus ointment is a time-honoured safe and effective drug used in the treatment of AD and AKC.^{15 16} In light of our experience, we suggest using this ointment as first line for significant dupilumab-induced blepharoconjunctivitis.

In their paper, Levine *et al* propose an algorithm for the treatment of DIOSD which does not mention tacrolimus ointment, and suggest to discontinue dupilumab or decrease its dose when conjunctivitis persists despite treatment.² Our results suggest that discontinuation of dupilumab because of DIOSD is probably unnecessary, and we believe that a trial of tacrolimus ointment should be attempted before discontinuation of dupilumab is considered.

In conclusion, DIOSD is common in patients with AD receiving dupilumab. Previous AKC is a risk factor for this complication while a family history of atopy might be a protective factor. While most cases are mild, some patients can develop severe blepharoconjunctivitis which is distinct from AKC and responds rapidly and extremely well to periocular tacrolimus ointment. With this treatment, the continuation of dupilumab therapy was possible in all of our patients with AD. Further studies might elucidate the pathological mechanisms responsible for DIOSD and assist in establishing a treatment algorithm for this complication.

Contributors YN, MM, EL, IB, EH and YAL: design and conduct of the study, collection, management, analysis and interpretation of the data. YN, MM, EL, IB, EH and YAL: statistics, preparation of the manuscript, management.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests EH and YAL were scientific advisors and speakers for Sanofi/Regeneron. Other authors declare no competing interests.

Patient consent for publication Obtained.

Ethics approval The study followed the tenets of the 1964 Declaration of Helsinki and was approved by the local ethics committee of Rabin Medical Center.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

- 1 Ou Z, Chen C, Chen A, *et al*. Adverse events of Dupilumab in adults with moderate-to-severe atopic dermatitis: a meta-analysis. *Int Immunopharmacol* 2018;54:303–10.
- 2 Levine RM, Tattersall IW, Gaudio PA, *et al*. Cicatrizing Blepharoconjunctivitis occurring during Dupilumab treatment and a proposed algorithm for its management. *JAMA Dermatol* 2018;154:1485–6.
- 3 Akinlade B, Guttman-Yassky E, Bruin-Weller M, *et al*. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019;181.
- 4 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.
- 5 Barnes AC, Blandford AD, Perry JD. Cicatricial ectropion in a patient treated with dupilumab. *Am J Ophthalmol Case Rep* 2017;7:120–2.
- 6 Shen E, Xie K, Jwo K, *et al*. Dupilumab-Induced follicular conjunctivitis. *Ocul Immunol Inflamm* 2018;1–3.
- 7 Simpson EL, Bieber T, Guttman-Yassky E, *et al*. Two phase 3 trials of Dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016;375:2335–48.
- 8 Blauvelt A, de Bruin-Weller M, Gooderham M, *et al*. Long-Term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (liberty AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *The Lancet* 2017;389:2287–303.
- 9 Wollenberg A, Ariens L, Thureau S, *et al*. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab—clinical characteristics and treatment. *J Allergy Clin Immunol* 2018;6:1778–80.
- 10 Thyssen JP, Bruin-Weller MS, Paller AS, *et al*. Conjunctivitis in atopic dermatitis patients with and without dupilumab therapy – international eczema Council survey and opinion. *J Eur Acad Dermatol Venereol* 2019;33:1224–31.
- 11 Bakker DS, Ariens LFM, van Luijk C, *et al*. Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis. *Br J Dermatol* 2019;180:1248–9.
- 12 de Bruin-Weller M, Graham NMH, Pirozzi G, *et al*. Could conjunctivitis in patients with atopic dermatitis treated with dupilumab be caused by colonization with *Demodex* and increased interleukin-17 levels?: reply from the authors. *Br J Dermatol* 2018;178:1220–1.
- 13 Wen H-J, Chen P-C, Chiang T-L, *et al*. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. *Br J Dermatol* 2009;161:1166–72.
- 14 Borkar DS, Gonzales JA, Tham VM, *et al*. Association between atopy and herpetic eye disease: results from the Pacific ocular inflammation study. *JAMA Ophthalmol* 2014;132:326–31.
- 15 Ohtsuki M, Morimoto H, Nakagawa H. Tacrolimus ointment for the treatment of adult and pediatric atopic dermatitis: review on safety and benefits. *J Dermatol* 2018;45:936–42.
- 16 Al-Amri AM. Long-Term follow-up of tacrolimus ointment for treatment of atopic keratoconjunctivitis. *Am J Ophthalmol* 2014;157:280–6.