Ocular allergy as a risk factor for dry eye in adults and children

Edoardo Villani[a,b], *Giovanni Rabbiolo*[a,b], *and Paolo Nucci*[a,b]

Purpose of review
To provide an overview of the pathogenic mechanisms underlying the correlation between ocular allergy and dry eye disease (DED), highlighting how the first condition may be a risk factor for the second one.

Recent findings
Recent advances in our comprehension of the pathogenesis of ocular allergy and DED allow identifying several pathways of interaction between these two conditions. A growing body of evidence supports the role of ocular allergy as a risk factor for DED. Ocular allergy, particularly the severe forms of keratoconjunctivitis, can impact on different key mechanisms of the DED vicious cycle, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities.

Summary
Ocular allergy and DED are two common, relevant, symptomatic, not mutually exclusive conditions affecting the ocular surface. They share some clinical and biochemical features. To better understand the complex interactions between these two conditions, it's essential to consider the very wide spectrum of clinical conditions included in the term ocular allergy and the still largely unexplored peculiarities of the pediatric ocular surface physio-pathology and DED.

Keywords
dry eye disease, inflammation, ocular allergy, ocular surface, pediatric

INTRODUCTION

In the daily clinical practice ocular allergy and dry eye disease (DED) are common and growing healthcare problems, with a significant negative impact on quality of life and productivity [1▪,2▪].

Epidemiological studies, made difficult by heterogeneity and lack of standardization of diseases' definitions and diagnostic algorithms [3▪,4▪], report prevalence ranges in the general population of 10–30% and 5–50%, respectively, for ocular allergy and DED [1▪,2▪]. However, although ocular allergy seems to affect more commonly children and adolescents [1▪,5], DED prevalence increases with age [2▪].

Ocular allergy and DED are different clinical entities affecting the ocular surface but their clinical manifestations include partly overlapping signs and symptoms [6]. The coexistence of these two conditions, hypothesized more than 20 years ago [7], has been confirmed to be a common circumstance by large cross-sectional studies [6]. Several studies tried to investigate the relationship between ocular allergy and DED, suggesting that the first one can predispose to the second one, and the Tear Film and Ocular Surface Society Dry Eye WorkShop II (TFOS DEWS II) recently included Allergic Conjunctivitis among the 'probable' (supported by suggestive evidence, implying the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information but either not published or published somewhere other than in a peer-reviewed journal) risk factors for DED [2▪].

The current article is aimed to provide a critical revision of new insights into the pathogenetic mechanisms of DED and how they can be affected by ocular allergy.

OCULAR ALLERGY IN ADULTS AND CHILDREN

Ocular allergy is a collection of ocular surface disorders, classically classified in two groups: common

[a]Department of Clinical Science and Community Health, University of Milan and [b]Eye Clinic San Giuseppe Hospital, IRCCS Multimedica, Milan, Italy

Correspondence to Edoardo Villani, MD, FEBO, Clinica Oculistica Ospedale San Giuseppe, via San Vittore 12, 20154 Milan, Italy.
Tel: +39 3397859677; e-mail: edoardo.villani@unimi.it

Curr Opin Allergy Clin Immunol 2018, 18:398–403
DOI:10.1097/ACI.0000000000000471

KEY POINTS

- Ocular allergy and DED are common and growing healthcare problems, with a significant negative impact on quality of life both in adults and children.
- Ocular allergy includes a very wide spectrum of clinical conditions, ranging from mild seasonal allergic conjunctivitis to severe and sight-threatening keratoconjunctivitis.
- A growing body of evidence support the role of ocular allergy as a risk factor for DED.
- Ocular allergy can impact on different key mechanisms of the DED vicious cycle, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities.
- The peculiarities of the pediatric ocular surface physiopathology, including ocular allergy and DED features, are still largely unexplored.

allergic conjunctivitis, including seasonal and perennial forms (SAC and PAC), and rarer keratoconjunctivitis, including vernal and atopic forms (VKC and AKC).

SAC and PAC are mild-to-moderate allergic disease, often associated with rhinitis, involving an IgE-mediated hypersensitivity response.

VKC and AKC are severe chronic inflammatory diseases of the ocular surface with a more complex pathogenesis that includes a T-helper-mediated response.

Ocular itching, swelling, and tearing are the most frequent symptoms complained by patients with all forms of ocular allergy, whereas photophobia and pain are typical of the most severe forms, due to the frequent (up to 70% of patients) corneal involvement, ranging from superficial punctate keratitis to ulcers and plaques [3▪,8].

The different types of ocular allergy have different ages of onset and characteristic age-related evolutions. SAC and PAC onset is usually during adolescence and young adulthood (80% of patients are younger than 30 years old), VKC is a paediatric disease, usually subsiding after puberty, whereas AKC symptoms may appear during childhood but the most frequent onset age ranges from 30 to 50 years old [3▪,5].

DRY EYE IN ADULTS AND CHILDREN

'Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological role' [9▪▪]. The newly revised definition of DED, proposed by the TFOS DEWS II, highlights the etio-pathogenetic role of five key mechanisms, providing a useful trace to investigate how ocular allergy could impact on DED pathogenesis (Fig. 1).

Pediatric dry eye has been historically considered as a rare condition, mainly associated with congenital, autoimmune, and inflammatory disorders, but it has not been investigated as well as in adults, and its diagnosis is often overlooked [10,11]. Recent evidences suggest that the peculiar, not yet fully understood, anatomo-physio-pathology of the pediatric ocular surface, the specific difficulties related to symptoms assessment and interpretation, and the lack of standardized and validated diagnostic strategies, have limited a lot our comprehension of this more neglected than rare disease [6,11–14].

OCULAR ALLERGY AND TEAR FILM INSTABILITY

A growing number of articles report the association between ocular allergy and decreased tear film break-up time (BUT). This phenomenon is more evident in allergic kerato-conjunctivitis, and it seems to be correlated with the severity of the ocular surface disease, as suggested by a comprehensive study published by Hu *et al.* [15] who reported a BUT of 3.1 ± 1.6 s vs. 4.5 ± 1.0 s vs. 11.4 ± 1.0 s ($P < 0.01$), respectively, in AKC, VKC, and healthy controls.

More recent studies, comparing children affected by SAC, PAC, and even allergic rhinitis to age-matched healthy individuals, demonstrated that also these conditions affect the tear film stability [12–14,16]. These articles provided essential information on this issue but, reporting very heterogeneous BUT values and adopting a threshold value of 10 s (validated only in adults), they also indirectly highlighted our current poor knowledge of pediatric dry eye.

Significantly, a few studies on tear film stability in intermittent forms of ocular allergy reported that VKC patients seem to show a shortened BUT even in the quiet phases of the disease [11], whereas SAC patients don't have decreased tear film stability outside the pollen season [17].

In the vicious cycle of DED, tear film instability may be due to different mechanisms, including meibomian glands and lipid layer changes on the one hand and mucins alterations on the other [18▪▪,19▪].

A few imaging studies assessed meibomian glands in different forms of ocular allergy [20▪], including AKC, VKC, and PAC. They showed

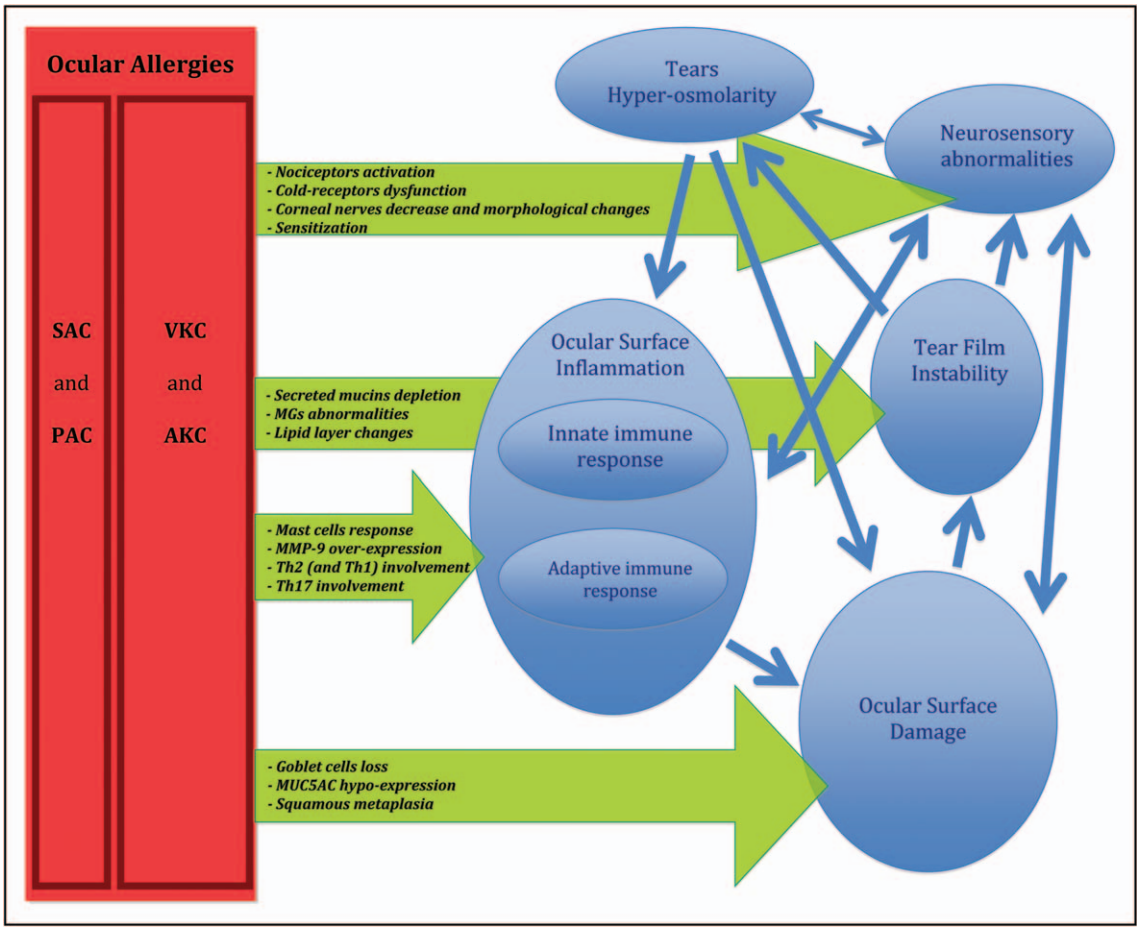

FIGURE 1. Scheme of the main pathways of impact of ocular allergy on dry eye disease vicious cycle. Seasonal allergic conjunctivitis and perennial allergic conjunctivitis subset is under-represented in the ocular allergy set because of the lower impact of these forms on the dry eye disease pathogenic mechanisms.

morphological changes, probably related partly to ocular surface inflammation and partly to continuous mechanical stress to the tarsal tissue by eye rubbing. Functional implications of these morphological changes have been suggested, but they need to be further investigated. Only one study, published more than 10 years ago by Suzuki *et al.* [21], assessed the alterations of the tear film lipid layer in ocular allergy. This research showed increased lipid layer thickness in patients with SAC and reported a surprising negative correlation between lipid layer thickness and BUT.

The impact of ocular allergy on secreted and membrane-associated mucins has been studied a bit more in depth, at least in severe forms.

Preclinical studies on mouse models suggested that histamine, leukotrienes, and prostaglandins directly stimulate goblet cell secretion, whereas inflammatory cytokines as IL-13, TNFα, and IFNγ have opposing effects on the regulation of secretion, proliferation, and apoptosis of these cells [22].

Several in-vivo studies from the Keio University reported a depletion of MUC5AC in patients with AKC and VKC [15,23], particularly in eyes with corneal shield ulcers [24]. The decreased tear concentration of this gel-forming mucin is widely accepted as a feature of all forms of DED [18▪▪].

OCULAR ALLERGY AND TEAR FILM HYPEROSMOLARITY

Hyperosmolarity of the tear film is a core mechanism of DED [18▪▪] and, thanks to the existence of a validated point-of-care tear film osmometer, it has been recently incorporated in the diagnostic algorithm proposed by the TFOS DEWS II [4▪].

The previously discussed impact of ocular allergy on tear film stability provides a strong rationale to hypothesize an effect of these conditions on tear film osmolarity, mediated by increased evaporation. However, at the moment, this issue has been investigated by a single uncontrolled study (level IV

of evidence) [25], which reported in eyes with acute allergic rhinoconjunctivitis mean values of tear osmolarity ranging from 318 and 324 mOsm/l, therefore higher than threshold adopted for diagnosis of DED (308 mOsm/l) [26].

OCULAR ALLERGY AND OCULAR SURFACE INFLAMMATION

Inflammation, including both innate immune response and adaptive response, is a key element of the DED vicious cycle. The acute response involves the mitogen-activated protein kinases and NF-κB signaling pathways, the generation of inflammatory cytokines as IL-1 and TNF-α, and the upregulation of matrix metalloproteinases (MMP) production by epithelial cells. The adaptive response is initiated by the activation and migration of resident antigen-presenting cells toward the regional draining lymphnodes, in which they stimulate naïve T cells (Th0), leading to the expansion of IL-17-γ and IFN-γ-secreting Th17 (Th17/1) cells [18▪▪,27▪▪].

The conjunctival allergic inflammatory response is associated with IgE-mediated mast cell activation leading to the release of preformed mediators including histamine and proteases (acute phase). The subsequent de novo formation of chemokines and cytokines triggers a cascade of cellular and molecular events leading to the recruitment and activation of eosinophils and of Th2 and Th1 lymphocytes (late phase) [28▪▪].

The role of Th17 in ocular allergy is controversial. Some researches reported preliminary data suggesting increased tear levels of IL-17 in VKC [29] and in SAC and PAC [30]. However, this does not directly point to a role for Th17 cells as other cells, innate immune cells, are also IL-17 producers [31]. Moreover, Fukushima *et al.* [32], in an experiment conducted on an animal model of allergic conjunctivitis, showed that wild type and IL-17$^{-/-}$ mice did not differ in conjunctival eosinophil infiltration.

Proteolytic enzymes, particularly MMP-9, play a key role in DED pathogenesis by disrupting intercellular epithelial tight junctions, leading to a breakdown of the ocular surface epithelial barrier [18▪▪]. MMP-9 has recently been proposed as one of the best DED severity biomarkers [33▪▪], and as a diagnostic biomarker, assessable by a point-of-care immunoassay [34].

Increased tears levels of MMP-1, MMP-2, and MMP-9, and increased ratio of MMPs to their tissue inhibitor have been well demonstrated in VKC and in a minority of patients with allergic conjunctivitis [35,36]. Significantly, in ocular allergy as in DED, MMP-9 showed a significant correlation with corneal epithelial damage.

OCULAR ALLERGY AND OCULAR SURFACE DAMAGE

Epithelial cells death, loss of goblet cells, and squamous cell metaplasia are well known key components of the DED vicious cycle, especially in advanced forms. This type of ocular surface damage is due to several concomitant elements, including frictional damage, hyperosmolar environment, and chronic inflammation with IFN-γ overexpression [18▪▪].

Several studies, using conjunctival impression and brush cytology to investigate the grade of metaplasia, the density of goblet cells and the level of secretory mucins (mainly MUC5AC) expression, clearly demonstrated squamous metaplasia in AKC and VKC. The ocular surface damage was correlated to severity and duration of the allergic inflammation, and it was negatively correlated to the tear film stability, probably because of a 'mucin-deficient dry eye state'. The over-expression of some membrane-associated mucins might be interpreted as a manifestation of an ocular surface defense response [15,22–24,37].

Mild forms of allergic conjunctivitis don't seem to induce this type of ocular surface damage [38].

OCULAR ALLERGY AND NEUROSENSORY ABNORMALITIES

The crucial role of neurosensory abnormalities in DED has been recently highlighted including them in the definition of the disease [9▪▪]. Tear film hyperosmolarity and instability and ocular surface inflammation are able to change the behavior of the different classes of corneal sensory receptors, inducing peripheral sensitization and, in the long term, inducing nerves damage. The peripheral ocular surface neuropathy can impact on several components of the morpho-functional unit, including tear secretion, blink rate, epithelial and goblet cells trophism, and the behavior of the corneal immune cells. Perpetuation of the vicious cycle can ultimately lead to central sensitization [18▪▪,39▪▪].

In DED patients, several clinical studies, using mechanical esthesiometry, showed a reduction of corneal sensitivity. Moreover, imaging studies using in-vivo confocal microscopy to assess the corneal subbasal nerves plexus, demonstrated a DED-related reduction of nerves density and increase of nerves tortuosity and subbasal immune cells density [39▪▪,40].

Similar researches reported similar results, with a few qualitative differences, also in AKC and VKC patients [40,41]. Interesting findings in severe ocular allergy included a good correlation between corneal sensitivity and subbasal nerves quantitative

and morphological changes, the correlation between corneal sensitivity and conjunctival goblet cells density, and the confocal demonstration of the presence of stromal nerves morphological abnormalities [15,23,40,41].

Ocular allergy and DED symptoms include a wide variety of unpleasant sensations, mainly mediated by the corneal sensory innervation. If itching and dryness are historically considered as pathognomonic of the two diseases, symptoms are often overlapping and include tearing, burning, foreign body sensation, and other types of discomfort [3▪,8,9▪▪,39▪▪].

Molecular and functional characteristics of corneal sensory innervation are not yet fully understood. However, ocular sensory neurons can be broadly classified as polymodal nociceptor neurons, cold thermoreceptor neurons, and selective mechano-nociceptor neurons [39▪▪,42]. Experimental evidences suggest that ocular allergy can evoke direct chemical activation and sensitization of polymodal nociceptors, discrete sensitization of mechano-nociceptors, and reduction of cold thermoreceptor activity [43], whereas in DED, the sensitization of polymodal and mechano-nociceptor nerve endings is combined with an abnormal increase in cold thermoreceptor activity [39▪▪].

ANTIALLERGIC TREATMENT AND IATROGENIC DRY EYE

Dry eye can be caused by a variety of iatrogenic interventions, including topical or systemic drugs, the use of contact lenses, and ophthalmic surgical and nonsurgical procedures.

Large population-based studies showed that systemic antihistamines are a risk factor for DED (odds ratio: 1.6). These drugs have anticholinergic activity and can affect G-protein coupled muscarinic receptors in the lacrimal gland acini and conjunctival secreting cells [44▪].

Topical drugs may affect the ocular surface determining allergic, toxic, and inflammatory effects by interaction with the tear film components, by tension-active effects, by reducing tear secretion, or by damaging goblet cells, epithelial cells, corneal nerves, and meibomian glands.

Several studies reported correlations between different topical antiallergic drugs, mainly epinastine and olopatadine, and DED. However, specific data on the active compounds are difficult to obtain because of the possible confounding role of preservatives and excipients [44▪].

About preservatives, the role of benzalkonium chloride in damaging the ocular surface has been largely studied [45].

CONCLUSION

In conclusion, ocular allergy and DED are two common, relevant, symptomatic, not mutually exclusive conditions affecting the ocular surface. They share some clinical and biochemical features.

If DED is a comprehensive term, including different types of patients, ocular allergy include a very wide spectrum of clinical conditions, ranging from mild-SAC-to-severe and sight-threatening keratoconjunctivitis.

Recent advances in the comprehension of DED pathogenic mechanisms allow identifying several pathways of interaction between these two conditions, providing a strong rationale to consider ocular allergy as a risk factor for DED (Fig. 1).

Ocular allergy have peculiar implications and manifestations in children. Further studies on this topic will help to better understand the several outstanding issues relating to pediatric ocular surface and DED.

Acknowledgements

We would like to thank Dr Marika Dello Strologo for her precious assistance with the article.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. Patel DS, Arunakirinathan M, Stuart A, Angunawela R. Allergic eye disease. ▪ BMJ 2017; 359:j4706.

The article provides essential information on ocular allergy, easily readable for different healthcare professionals.

2. Stapleton F, Alves M, Bunya VY, *et al.* TFOS DEWS II epidemiology report. ▪ Ocul Surf 2017; 15:334–365.

The article, result of an evidence-based group effort, summarizes the available knowledge on the prevalence, incidence, risk factors, natural history, and morbidity of dry eye disease (DED).

3. Leonardi A, Doan S, Fauquert JL, *et al.* Diagnostic tools in ocular allergy. ▪ Allergy 2017; 72:1485–1498.

The position paper provides a comprehensive overview of the currently available tools for diagnosing ocular allergy to promote a common nomenclature and procedures to be used by different specialists.

4. Wolffsohn JS, Arita R, Chalmers R, *et al.* TFOS DEWS II diagnostic meth- ▪ odology report. Ocul Surf 2017; 15:539–574.

The article, result of an evidence-based group effort, proposes a consensus on the most efficacious battery of tests for diagnosing and monitoring DED and on the most appropriate order and technique to conduct these tests in a clinical setting.

5. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. Curr Opin Allergy Clin Immunol 2015; 15:482–488.
6. Hom MM, Nguyen AL, Bielory L. Allergic conjunctivitis and dry eye syndrome. Ann Allergy Asthma Immunol 2012; 108:163–166.
7. Toda I, Shimazaki J, Tsubota K. Dry eye with only decreased tear break-up time is sometimes associated with allergic conjunctivitis. Ophthalmology 1995; 102:302–309.

8. Sacchetti M, Abicca I, Bruscolini A, *et al.* Allergic conjunctivitis: current concepts on pathogenesis and management. J Biol Regul Homeost Agents 2018; 32(1 Suppl. 1):49–60.
9. ■■ Craig JP, Nichols KK, Akpek EK, *et al.* TFOS DEWS II definition and classification report. Ocul Surf 2017; 15:276–283.

The article, result of an evidence-based group effort, proposes a consensus on updated definition and classification of DED. This work may have a great impact on future researches on the topic.

10. Alves M, Dias AC, Rocha EM. Dry eye in childhood: epidemiological and clinical aspects. Ocul Surf 2008; 6:44–51.
11. Villani E, Dello Strologo M, Pichi F, *et al.* Dry eye in vernal keratoconjunctivitis: a cross-sectional comparative study. Medicine (Baltimore) 2015; 94:e1648.
12. Chen L, Pi L, Fang J, *et al.* High incidence of dry eye in young children with allergic conjunctivitis in Southwest China. Acta Ophthalmol 2016; 94:e727–e730.
13. Akil H, Celik F, Ulas F, Kara IS. Dry eye syndrome and allergic conjunctivitis in the pediatric population. Middle East Afr J Ophthalmol 2015; 22:467–471.
14. Kim TH, Moon NJ. Clinical correlations of dry eye syndrome and allergic conjunctivitis in Korean children. J Pediatr Ophthalmol Strabismus 2013; 50:124–127.
15. Hu Y, Matsumoto Y, Dogru M, *et al.* The differences of tear function and ocular surface findings in patients with atopic keratoconjunctivitis and vernal keratoconjunctivitis. Allergy 2007; 62:917–925.
16. Dogru M, Gunay M, Celik G, Aktas A. Evaluation of the tear film instability in children with allergic diseases. Cutan Ocul Toxicol 2016; 35:49–52.
17. Kosina-Hagyó K, Veres A, Fodor E, *et al.* Tear film function in patients with seasonal allergic conjunctivitis outside the pollen season. Int Arch Allergy Immunol 2012; 157:81–88.
18. ■■ Bron AJ, de Paiva CS, Chauhan SK, *et al.* TFOS DEWS II pathophysiology report. Ocul Surf 2017; 15:438–510.

The article, result of an evidence-based group effort, summarizes the available knowledge on the pathogenesis of DED and proposes a revised scheme of the DED vicious cycle.

19. ■ Willcox MDP, Argüeso P, Georgiev GA, *et al.* TFOS DEWS II tear film report. Ocul Surf 2017; 15:366–403.

The article, result of an evidence-based group effort, summarizes the available knowledge on biophysical and biochemical aspects of tears and how these change in DED.

20. ■ Mizoguchi S, Iwanishi H, Arita R, *et al.* Ocular surface inflammation impairs structure and function of meibomian gland. Exp Eye Res 2017; 163:78–84.

The article shows that ocular surface and palpebral conjunctival including eyelid margin inflammation is associated with alteration in meibomian gland structure and potentially function.

21. Suzuki S, Goto E, Dogru M, *et al.* Tear film lipid layer alterations in allergic conjunctivitis. Cornea 2006; 25:277–280.
22. Dartt DA, Masli S. Conjunctival epithelial and goblet cell function in chronic inflammation and ocular allergic inflammation. Curr Opin Allergy Clin Immunol 2014; 14:464–470.
23. Dogru M, Matsumoto Y, Okada N, *et al.* Alterations of the ocular surface epithelial MUC16 and goblet cell MUC5AC in patients with atopic keratoconjunctivitis. Allergy 2008; 63:1324–1334.
24. Dogru M, Asano-Kato N, Tanaka M, *et al.* Ocular surface and MUC5AC alterations in atopic patients with corneal shield ulcers. Curr Eye Res 2005; 30:897–908.
25. Oxford Centre for Evidence-Based Medicine – level of evidence (March 2009). Available at: http://www.cebm.net/index.aspx?o=1025. [Accessed 1 June 2018].
26. Nitoda E, Lavaris A, Laios K, *et al.* Tear film osmolarity in subjects with acute allergic rhinoconjunctivitis. In Vivo 2018; 32:403–408.
27. ■■ Chen Y, Chauhan SK, Shao C, *et al.* IFN-γ-expressing Th17 cells are required for development of severe ocular surface autoimmunity. J Immunol 2017; 199:1163–1169.

The study demonstrates that Th17 cells mediate ocular surface autoimmunity through both IL-17A and IFN-γ. These findings are essential to clarify the doubts on the role of Th1 cells in DED pathogenesis.

28. ■■ Elieh Ali Komi D, Rambasek T, Bielory L. Clinical implications of mast cell involvement in allergic conjunctivitis. Allergy 2018; 73:528–539.

The article summarize the new insights on ocular allergy pathogenesis, providing essential information for future researches on the topic and to understand the clinical behavior of the different types of ocular allergy.

29. Validad MH, Khazaei HA, Pishjoo M, Safdari Z. The study of interleukin-17 level in vernal keratoconjunctivitis disease and its relationship between symptom and sign severity. Semin Ophthalmol 2017; 32: 721–724.
30. Yan A, Luo G, Zhou Z, *et al.* Tear osteopontin level and its relationship with local Th1/Th2/Th17/Treg cytokines in children with allergic conjunctivitis. Allergol Immunopathol (Madr) 2018; 46:144–148.
31. Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol 2010; 10:479–489.
32. Fukushima A, Sumi T, Ishida W, *et al.* Endogenous IL-17 does not play a significant role in the development of experimental murine allergic conjunctivitis. Int Arch Allergy Immunol 2008; 147:206–212.
33. ■■ Pinto-Fraga J, Enríquez-de-Salamanca A, Calonge M, *et al.* Severity, therapeutic, and activity tear biomarkers in dry eye disease: a clinical-trial subanalysis. Ocul Surf 2018; 16:368–376.

The clinical-trial subanalysis identified different biomarkers for DED. These information may have important consequences on the design of future clinical trials on DED.

34. Messmer EM, von Lindenfels V, Garbe A, Kampik A. Matrix metalloproteinase 9 testing in dry eye disease using a commercially available point-of-care immunoassay. Ophthalmology 2016; 123:2300–2308.
35. Leonardi A, Brun P, Abatangelo G, *et al.* Tear levels and activity of matrix metalloproteinase (MMP)-1 and MMP-9 in vernal keratoconjunctivitis. Invest Ophthalmol Vis Sci 2003; 44:3052–3058.
36. Kumagai N, Yamamoto K, Fukuda K, *et al.* Active matrix metalloproteinases in the tear fluid of individuals with vernal keratoconjunctivitis. J Allergy Clin Immunol 2002; 110:489–491.
37. Onguchi T, Dogru M, Okada N, *et al.* The impact of the onset time of atopic keratoconjunctivitis on the tear function and ocular surface findings. Am J Ophthalmol 2006; 141:569–571.
38. Uchida H, Imanaga Y. Effect of mild conjunctivitis complication on tear balance in dry eye. Cont Lens Anterior Eye 2012; 35:240–242.
39. ■■ Belmonte C, Nichols JJ, Cox SM, *et al.* TFOS DEWS II pain and sensation report. Ocul Surf 2017; 15:404–437.

The article, result of an evidence-based group effort, summarizes the available knowledge on the neurobiological mechanisms that underpin discomfort accompanying DED and provides essential information on the methods available for the experimental and clinical exploration in humans of the neurobiological parameters involved in DED symptoms.

40. Villani E, Mantelli F, Nucci P. In-vivo confocal microscopy of the ocular surface: ocular allergy and dry eye. Curr Opin Allergy Clin Immunol 2013; 13:569–576.
41. Leonardi A, Lazzarini D, Bortolotti M, *et al.* Corneal confocal microscopy in patients with vernal keratoconjunctivitis. Ophthalmology 2012; 119:509–515.
42. Belmonte C, Aracil A, Acosta MC, *et al.* Nerves and sensations from the eye surface. Ocular Surf 2004; 2:248–253.
43. Acosta MC, Luna C, Quirce S, *et al.* Changes in sensory activity of ocular surface sensory nerves during allergic keratoconjunctivitis. Pain 2013; 154:2353–2362.
44. ■ Gomes JAP, Azar DT, Baudouin C, *et al.* TFOS DEWS II iatrogenic report. Ocul Surf 2017; 15:511–538.

The article, result of an evidence-based group effort, summarizes the available knowledge on iatrogenic DED and it presents future directions to address this growing issue.

45. Baudouin C, Labbé A, Liang H, *et al.* Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res 2010; 29:312–334.