

EDITORIAL

Vernal keratoconjunctivitis: evidence for immunoglobulin E-dependent and immunoglobulin E-independent eosinophilia

Introduction

Vernal conjunctivitis is a Th2 lymphocyte-driven chronic allergic disease that compromises vision. Corneal ulceration and neovascularization is a frequent consequence of chronic disease, and existing treatments for the disease are not satisfactory. Hyperaemia and papillae formation are hallmarks of the disease, and these are associated with massive infiltration of the conjunctiva by multiple inflammatory cells. Whilst T cells, mast cells and neutrophils are all recruited to the conjunctiva in vernal keratoconjunctivitis (VKC) patients, the eosinophil is the most prominent and consistent inflammatory cell observed in this disease. Recently, there has been considerable progress in the understanding of the pathophysiology of this disease. Whilst there are clear similarities with asthma, dermatitis and rhinitis, the accumulated data indicate that there are unique features of VKC – especially with respect to mechanisms of eosinophil recruitment. This information provides lessons in the biology of eosinophil recruitment and has implications for the therapy of ocular allergy.

Allergic reactions in the eye can be roughly subdivided into seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), atopic keratoconjunctivitis (AKC), giant-papillary conjunctivitis (GPC) and VKC. These conditions stem from transient phenomena that clear rapidly after allergen exposure (i.e. in mild SAC), to chronic diseases that both cause considerable discomfort and obscure vision [1]. Whilst the conditions vary considerably in their severity and pathogenesis, each occurs most frequently in atopic individuals (Figure 1).

Several lines of evidence indicate that Th2 lymphocyte-driven, IgE-dependent type I hypersensitivity reactions underlie the pathogenesis of this group of conditions [2]. First, there is significant cosegregation of these diseases with other allergic diseases (e.g. rhinitis, asthma, dermatitis and food allergy). This indicates that general atopy genes may predispose individuals to develop any of a number of allergic conditions. The linkage mapping of both shared and distinct regions of the human genome in different allergic diseases supports this concept, albeit also providing evidence for disease-specific susceptibility loci [3–5]. Second, there is a strong correlation between the number of mast cells detected in the epithelium and substantia propria of the conjunctiva and disease severity. Third, these diseases either follow allergen exposure, or are a consequence of prolonged allergen exposure. Fourth, analysis of tears from patients with conjunctivitis usually reveals high levels of mast cell mediators and proteases during ongoing disease. Finally, mast cell stabilizers (such as nedocromil) both decrease clinical symptoms and the number of inflammatory cells resident in the conjunctiva.

The severity of allergic responses in the eye correlates well with the degree of eosinophilia in the late-phase reaction (when this does occur; Fig. 2). Thus, strong acute responses in SAC usually include significant eosinophilia, whilst mild early responses often lack any evidence of a late-phase reaction, and little or no eosinophilia. This is also true for AKC, GPC and VKC [6]. For this reason, it is not surprising that the levels of eosinophil cationic protein found in the tears of VKC patients correlates well with other established ophthalmic criteria for disease severity. All of these data suggest that the eosinophil may play an important role in the pathogenesis of ocular allergy. Despite this, there is very little known about the pathways that recruit eosinophils into the conjunctiva, and no direct assessment of the importance of eosinophils in disease pathogenesis.

A paper published in this issue of the Journal provides new insight into eosinophilia in ocular allergy which may also be useful for our understanding of eosinophilia in other allergic diseases [7]. Vierucci and coworkers have carefully studied 110 caucasian children with VKC and evaluated disease severity, evidence of allergen-sensitization, peripheral blood eosinophil counts and serum eosinophil cationic protein levels in these and control patients. The striking finding in their work is that whilst eosinophilia does clearly correlate with disease severity, there is no strict requirement for atopy or allergen-specific sensitization for the eosinophilic response. Indeed, while tarsal and mixed forms of conjunctivitis showed a correlation with total and allergen-specific IgE titres and skin tests, bulbar forms of VKC showed no such correlation. These data suggest that it is likely that there are both IgE-dependent and IgE-independent pathways driving eosinophilia in these two forms of VKC, and that eosinophils in the absence of a mast cell-driven response (in the bulbar forms) are sufficient to drive severe clinical symptoms in this mucosal tissue.

The first finding is important as a genetic study of individuals with bulbar forms of VKC may result in the identification of potentially new pathways driving eosinophilia in this (and potentially other) tissue(s). The second implication (that the observed eosinophilia in non-sensitized individuals can still drive VKC pathology) provides support for the view that the eosinophil is an important effector cell in allergic diseases. Since this view has been challenged over the past few years in interpretations of antibody therapy trials in humans (where asthma phenotypes remain despite greatly diminished eosinophil numbers), it is important to integrate the data in this paper into our evolving perspective on the role of the eosinophil in disease pathogenesis [8–10]. A closer inspection of the degree of eosinophilia in the antibody-treated asthmatics does indicate that there are residual eosinophils. Taken together, the data may actually imply very few eosinophils are needed to contribute to disease pathogenesis.

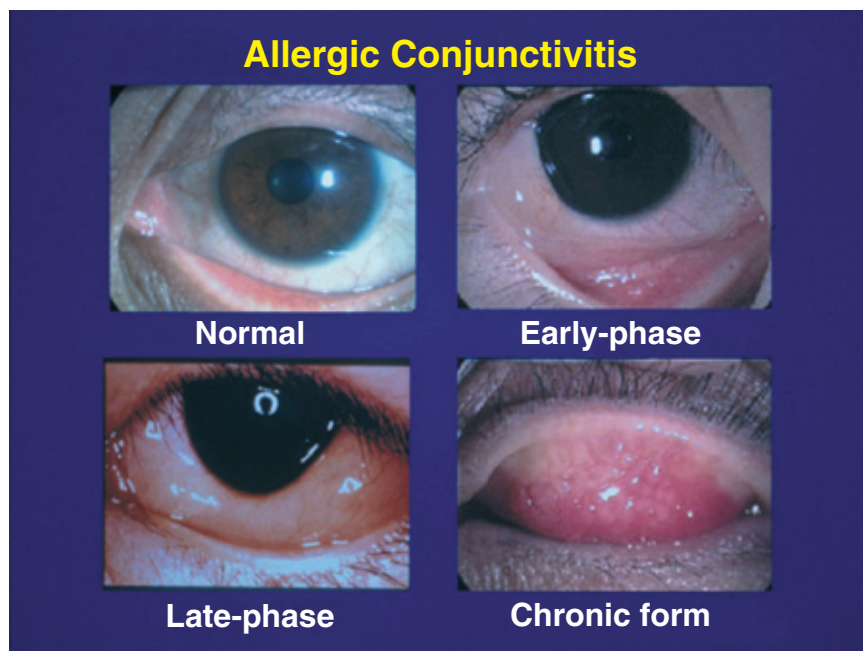


Fig. 1. Allergic inflammation in the human eye. Representative photos of normal, early-phase reaction, late-phase reaction and chronic allergic responses in the human eye.

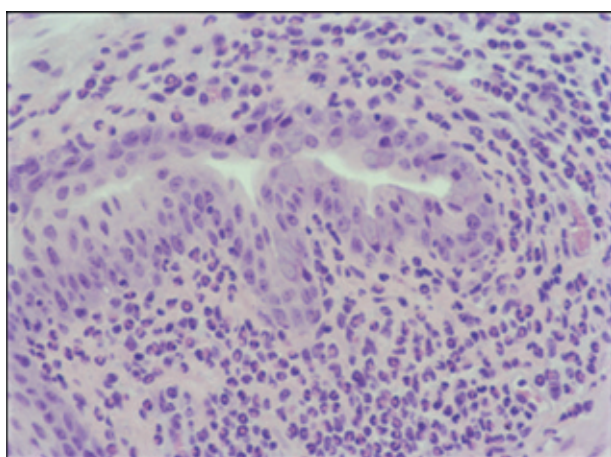


Fig. 2. The typical histology of a late-phase reaction in our mouse model of allergic conjunctivitis (a low magnification histology slide showing eosinophilia and neutrophilia in the conjunctiva in this animal model). This is also typically seen in moderate to severe cases of seasonal and chronic allergic conjunctivitis and vernal keratoconjunctivitis in humans.

The other points that now need to be addressed are: 1. What drives IgE-dependent eosinophilia in the conjunctiva; and 2. What interventions might be effective in inhibiting eosinophilia in the eye?

Our own analyses of chemokine gene expression in a murine model of allergic conjunctivitis have shown that several beta-chemokines are induced in the conjunctiva after allergen challenge [11, 12]. As is the case in other tissues, the chemokines that are induced locally are expressed at low (albeit detectable levels) in 'resting tissue' but are strongly and rapidly up-regulated upon allergen challenge. Several cell types are able to produce chemokines upon allergen exposure, including: endothelial cells, mononuclear cells, macrophages and resident mast cells [13, 14]. Some of these clearly drive IgE-dependent eosinophilia in ocular allergies. It will be of interest to compare and contrast

the portfolio of chemokines produced upon allergen exposure in the conjunctiva vs. the lung, skin, etc. (Fig. 3).

What chemokines (if any) are produced in the conjunctiva of VKC patients that are not atopic and have no evidence of sensitization to specific allergens? If chemokines are found in the tears of these patients, what mechanisms trigger this expression and which cells produce the chemokines?

One likely candidate for an important cellular source for chemokine expression is the antigen-presenting cell. It is already established that dendritic cells can express certain chemokines upon ligation of surface-bound IgE, and this might trigger chemokine expression from these cells in the IgE-dependent pathway [15]. This FcεRI-mediated activation pathway is also likely to be operative in resident mast cells that have also been shown to express chemokines upon IgE cross-linking [16].

If chemokines are expressed constitutively in the conjunctiva of VKC patients that show no signs of IgE-sensitization, it will be important to understand why this is the case. Are the factors produced from the nearby endothelium or epithelium that activate antigen-presenting cells *in situ* able to constitutively express eosinophil chemoattractants such as RANTES or eotaxin-1?

What are the molecular tools that might be exploited to inhibit eosinophilia in ocular allergy? First, as we have previously shown, blockade of APC activation by IL-1 receptor antagonist both extinguishes chemokine production and acute- and late-phase responses in our model of ocular allergy. Compounds targeted at the APC may therefore be useful in humans as well. Second, antibodies that might neutralize chemokines found to be important in driving conjunctival eosinophilia may be useful in the treatment of ocular allergy. Finally, targeting of chemokine receptors (especially CCR3) may be effective in ocular allergy.

I suspect the major take home lesson to this body of work should be that it is very important to study each allergic disease independently, as there are clearly both similarities and differences in the pathogenetic mechanisms operating in different mucosal tissues. Thus, findings in ocular allergy may be helpful

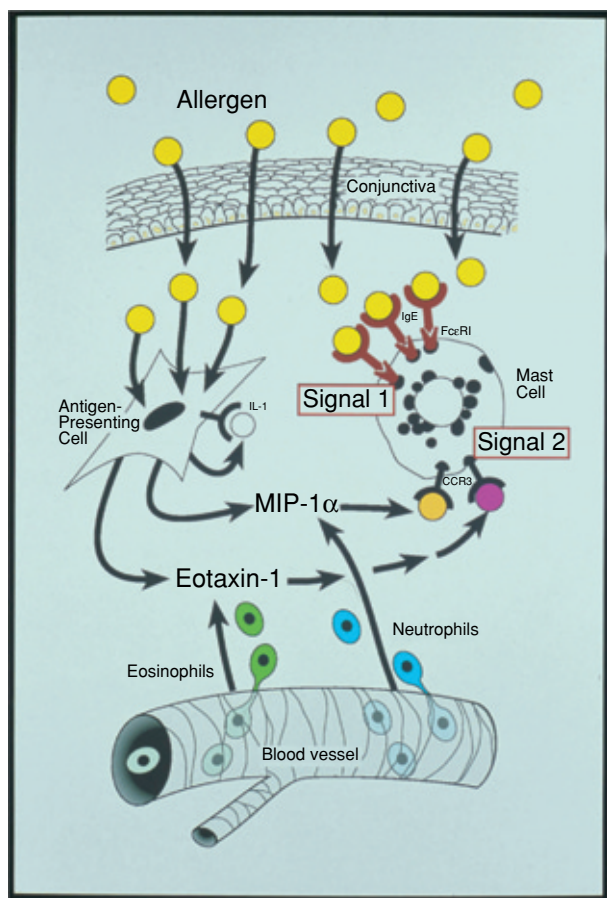


Fig. 3. A model of early chemokine (eotaxin and MIP-1 α) production in the inflamed eye. The diagram shows the important role chemokines play in the chemotaxis of neutrophils and eosinophils observed in the late-phase reaction, and the proposed direct affect of the chemokines on mast cell activation in the conjunctiva. The source of early chemokines is shown as antigen-presenting cells, but other cell types have been shown to be important sources of chemokine production in other tissues such as lung and skin. It will be important to understand the similarities and differences in these pathways in IgE-dependent and IgE-independent eosinophilia in human disease.

in resolving controversial issues in pulmonary allergy, e.g. the importance of the eosinophil as an effector vs. bystander cell. At the same time, the differences in the responses in tissues may render certain interventions effective in one, and totally ineffective in another. For example, targeting a particular chemokine or receptor may be very effective in the treatment of ocular allergy, while having no affect in the lung. The trick will be to keep a pulse on the unfolding mechanisms in different fields and to make use of the right mix of information in our synthesis of the biology of the allergic response.

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S. J. ONO
University College London
Institute of Ophthalmology
11–43 Bath Street
London, EC1V 9EL
UK
E-mail: santa.ono@ucl.ac.uk