Immune Mechanisms, Pathology, and Management of Allergic Ocular Diseases

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Abstract Allergic eye diseases are mediated primarily by immunoglobulin E (IgE) and/or Th2 cells along with cytokines, chemokines, histamine, prostaglandins, and leukotrienes that participate in the immunopathogenesis and immunopathology. Dendritic cells initiate the immune response to allergens by processing and presenting them as peptides to naïve T cells, which in turn, develops into allergen-specific Th2 cells that play a crucial role in the allergic immune process via action of Th2-derived cytokines that induce B cells to become allergen-specific IgE-producing plasma cells. This chapter provides a comprehensive review of the current understanding of the immunopathogenesis and immunopathology of allergic eye diseases including allergic conjunctivitis, giant papillary conjunctivitis, atopic keratoconjunctivitis, and vernal keratoconjunctivitis. The immunopathological process is responsible for the clinical manifestations of allergic eye diseases as well as damage and remodeling of the ocular surface. Furthermore, the role of immune cells and mediators in allergic ocular surface inflammation will be discussed in great detail with particular focus on T cells, eosinophils, mast cells, histamine, cytokines, chemokines, and eosinophil-derived mediators. Finally, clinical management of allergic eye diseases with pharmacotherapy that targets cells and mediators of allergic eye diseases as well as potential future therapeutic directions such as potential adjunctive therapeutic benefits of resident ocular microbiome that modulate the ocular mucosal immunity will be discussed. The main objective of this chapter is to highlight the immunopathology of allergic eye disease with a view to focus interest in developing therapeutic agents that target cells and mediators of allergic immune response and consequential immunopathological processes.

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1 Introduction

The eye is an important sensory organ of the human body that participates in the process of detecting visual stimuli, which subsequently undergo neural processing in the retina and brain [1]. However, the normal function of the eye could be affected by both infectious and non-infectious diseases along with the associated inflammatory state that develops in response to these threats. The ocular surface of the eye is exposed to the external environment with obvious threats from infection, trauma, and immunogenic factors of particular concern. Infectious and non-infectious diseases that affect the conjunctiva and cornea are listed in Table 1. The focus of this chapter is on allergic eye diseases with particular emphasis on the immunopathogenesis and immunopathological mechanisms. It is noteworthy that the immune system functions to distinguish between self and nonself, and as such, it tolerates self-antigens but recognize and remove non-self-antigens. However, innocuous substances can generate immunological memory following first encounter, and subsequently cause inflammation and tissue damage on re-exposure to the inciting innocuous substance. Overreaction of the adaptive immune system to innocuous environmental antigens along with associated inflammation and damage to the tissue are characteristics of the allergic immune response. Allergic eye diseases are predominantly due to type I hypersensitivity reactions triggered by allergen-specific

Table 1 Diseases of the conjunctiva and cornea

Diseases of the conjunctiva	Diseases of the cornea
Acute bacterial conjunctivitis	Fungal keratitis
Staphylococcal marginal keratitis	Bacterial keratitis
Follicular conjunctivitis	Acanthamoeba keratitis
Pharyngoconjunctival fever	Microsporidial keratoconjunctivitis
Acute hemorrhagic conjunctivitis	Herpes simplex keratitis
Epidemic keratoconjunctivitis	
Herpes simplex conjunctivitis	
Acute hemorrhagic conjunctivitis	
Trachoma	
Chemical conjunctivitis	Peripheral ulcerative keratitis
Amyloidosis conjunctivitis	Vernal keratoconjunctivitis
Toxic follicular conjunctivitis	Thygeson's superficial punctate keratitis
Cicatricial conjunctivitis	Superior limbic keratoconjunctivitis
Allergic conjunctivitis	Interstitial keratitis
Phlyctenular keratoconjunctivitis	Mooren's ulcer
Giant papillary conjunctivitis	Neurothrophic keratitis

IgE bound to Ig-like domain of the alpha chain of high affinity IgE receptor type 1 (FcεRI) on sensitized mast cells and basophils. There is also a type IV hypersensitivity reaction component in allergic eye disease, in which the chronic nature of the clinical manifestation of allergic eye disease is mediated predominantly by Th2 cells. Approximately 40% of individuals in the Western world are atopic with incidence of allergy on the increase in people who reside in developed nations [2]. Allergic eye diseases can be acute or chronic based on the underlying immunopathology and clinical manifestations of the allergen-induced immune response. The acute form includes allergic conjunctivitis (AC), which is predominantly a type I hypersensitivity response to innocuous substances such as allergens. The chronic form includes vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). Giant papillary conjunctivitis (GPC) has an immunological component to its pathogenesis; however, it is mostly due to microtrauma of the palpebral conjunctiva. Pollen is a major environmental aeroallergen associated with seasonal form of AC while dust mites and molds are indoor allergens associated with the perennial form of AC. Dendritic cells (DC), the initiator of the immune response to allergens, process and present allergen peptides to naïve T cells, which in turn, become activated to undergo proliferation and differentiation into allergen-specific Th2 cells that play a crucial role in allergic immune process via action of Th2-derived cytokines that induce allergen-specific B cells to proliferate and differentiate into allergen-specific IgE-producing plasma cells. The major effector cell involved in inducing the clinical manifestations of the allergen-induced immune response is the mast cell and its mediators such as histamine, tryptase, leukotrienes, prostaglandins, cytokines, and chemokines. Clinical manifestations of allergic eye disease include itching, tearing, eyelid edema, hyperemia, chemosis, papillary hypertrophy, corneal epithelial defects, and remodeling of the ocular surface. The management of allergic eye disease includes nonpharmacological and pharmacological therapy. Pharmacological therapy includes antihistamine, mast cell stabilizers, multimodal anti-allergic agents, and corticosteroids [3, 4].

This topic will discuss the immunology of the ocular surface with particular emphasis on conjunctival-associated lymphoid tissue (CALT), immunoregulation of the ocular surface, and factors that contribute to the immune privilege status of the cornea. Additionally, cells and mediators that play a role in the immunopathogenesis and immunopathology of allergic eye diseases will be discussed in detail with greater focus on antigen-presenting cells of the ocular surface, the part played by epithelial cells and fibroblasts in allergic eye diseases, the role of eosinophils and mast cells and their mediators, and the central role of Th2 cells and Th2-derived cytokines. Furthermore, the immune mechanisms of AC as a disease are characterized by IgE-mediated mast cell degranulation, which occurs in three successive stages (sensitization, early phase, late phase) will be discussed. Moreover, the multifactorial nature of the immune and pathological mechanisms of VKC and AKC along with the T cell-mediated immune mechanisms will be reviewed. There will also be a brief discussion of the immunological and mechanical aspects of the pathological mechanisms of GPC involving the actions of Th2 cells. Finally, in the end, approved and pipeline anti- allergic agents will be discussed.

2 Cells and Mediators of Allergic Eye Diseases

2.1 Allergens

Allergens are small antigens that are capable of diffusing across the mucosal surface to induce Th2 cell-mediated response that is characteristic of allergic eye diseases [5]. House dust mites, molds, and pollen allergens possess proteolytic enzymatic activity that promote allergenicity [6]. House dust mites are indoor allergens that possess cysteine and serine protease activity [7]. It is noteworthy that Dermatophagoides pteronyssinus 1 (Der p 1) and Der p 3 produce cysteine protease, whereas Der p 6 and Der p 9 allergens secrete serine protease [6]. Proteolytic enzymes released by allergens disrupt the barrier function of the conjunctival epithelium, this in turn, facilitates the access of allergen into the conjunctival subepithelial layer where it is taken up by antigen-presenting cell (APC), such as DCs that become activated to initiate the generation of allergen-specific Th2 cells and allergen-specific IgE [5, 7–9]. Thus, proteolytic enzymes produced by allergens play an important role in the pathogenesis of allergic eye disease, since it enhances the access of allergens to APCs in the conjunctiva epithelium and subepithelial layer, which in turn, facilitates the differentiation of naive T cells into allergen-specific T cells [6]. Allergens in contact with epithelial cells can trigger these cells to express thymic stromal lymphopoietin (TSLP), an IL-7-like epithelial cell-derived pro-allergic cytokine that activates DCs to promote the generation of Th2 cell immune response and associated allergic inflammation via TSLP-TSLPR (TSLP receptor chain) signaling pathways [10]. Additionally, mast cells, fibroblasts, and DCs can also secrete TSLP [11]. TSLP can activate eosinophils to express ICAM-1, which in turn, enhances the adhesion of eosinophils to vascular endothelium and its influx into the site of allergic inflammation [12]. Thus, TSLP has a role to play in the immunopathogenesis of allergic eye disease through the activation of DCs, eosinophils or mast cells in synergy with proinflammatory cytokines such as IL-1 and TNF-α [13, 14].

2.2 Antigen Presenting Cells

Antigen presenting cells (APCs) are cells that are capable of engulfing antigens and subsequently processing and presenting it on major histocompatibility complex (MHC) molecules as a peptide:MHC complex that is recognized by T cells [15, 16]. MHC is a cell surface molecule that plays a crucial role in displaying processed antigens in a form that is recognized by T cells [17, 18]. Nucleated cells express MHC class I molecules that present peptide antigen to $CD8^+$T cell; however, B cells, dendritic cells, and macrophages express MHC class II molecules that present peptide antigen to $CD4^+$T cell [19]. APCs bear costimulatory molecules that interact with costimulatory ligands on naïve T cells to provide co-stimulatory/survival signals during the process of T cell activation [20]. APCs are classified into professional and nonprofessional APCs based

on the level of constitutive expression of MHC class II molecules. DCs, macrophages and B cells are professional APCs that express high levels of MHC II antigen and costimulatory molecules. Nonprofessional APCs such as vascular endothelial cells, epithelial cells, and fibroblasts do not constitutively express costimulatory and MHC class II molecules, but these are upregulated when induced by pro-inflammatory mediators [21, 22]. Langerhans' cells are immature DCs located in the epithelium of the conjunctiva, limbus, and cornea. They take up antigen to become mature Langerhans' cells expressing MHC class II-positive with $CD80^+$ and $CD86^+$ that interact with naïve T cells to mediate Th2 cell polarization [23–25]. Conventional DCs are important APCs found in peripheral tissues including the cornea and conjunctiva. They are involved in the initiation and modulation of the allergic response, as well as in determining the nature of the immune response to allergens [23]. Immature DC take up antigen to undergo the maturation process to become mature DCs displaying processed peptide antigen and upregulating the expression of CCR7, CD80, and CD86. CCL21-CCR7 interaction directs chemokine-mediated migration of mature DCs to regional lymph nodes [12, 21]. Toll-like receptors (TLRs) are glycoprotein cell receptors that recognize exogenous and endogenous molecules. It is a pattern recognition receptor that triggers an innate immune response, which culminates in linking the innate and adaptive arms of the immune system [22, 26]. TLRs are expressed on non-immune cells such as epithelial cells and immune cells such as eosinophils, neutrophils, macrophages, monocytes, and DCs. TLR2, TLR4, and TLR6 are expressed on mast cells. TLR2- and TLR4-mediated mast cell degranulation is associated with the release of inflammatory mediators that may exacerbate inflammatory response in chronic allergic eye diseases such as atopic keratoconjunctivitis [26, 27]. TLRs located on DCs play an essential role as an innate immune surveillance system that initiates the innate immune response in the eye as well as induces the development of humoral and cellular immune responses [28]. Because DCs detect and present allergens to naïve T cells in regional secondary lymphoid organs with the intent of linking the innate and adaptive immune systems, they play an essential role in the proliferation and differentiation of naive T cells into effector T cells that participate in the allergic immune response of the ocular surface [19, 29].

2.3 T Cells

T cells are immune cells produced by common lymphoid progenitor cells in the bone marrow that undergo development and maturation in the thymus. These immune cells play an important role in generating an adaptive immune response to mediate antigen-specific effector immune responses and regulate activity of other immune and non-immune cells via the action of T cell-derived cytokines [18, 30]. The three crucial roles of effector T cells include killing, activation, and regulation [19, 31]. $CD8^+$T cells differentiate into cytotoxic T-lymphocytes that destroy intracellular pathogens especially viruses [25] while CD4T cells differentiate into Th1, Th2, Th17, and regulatory T cells [32]. $CD4^+$T helper cells provide signals in the form of cytokines that activate antigen-specific B cells, macrophages, and $CD8^+$T cells [25].

2.4 Cytokines

Cytokines are highly potent proteins secreted by immune and nonimmune cells that mediate cell division, inflammation, cytotoxicity, differentiation, migration, and repair. Cytokines include interleukins (ILs), colony stimulating factors (CSF), tumor necrosis factor (TNF), and interferons (IFN) [31]. IL-l (IL-lα and IL-lβ) is an important pro-inflammatory cytokine produced by immune (e.g. macrophage) and non-immune cells (e.g. epithelial cells). It plays a role in the immunopathogenesis of allergic disease [31, 33]. IL-2 facilitates the proliferation of activated T cells and B cells [25, 31, 34]. IL-4 is produced by Th2 cells and mast cells and it induces the production of IgE-secreting plasma cells [25, 31]. IL-13 is produced by Th2 cells and mast cells, and it induces the synthesis of IgE [31]. IL-4 and IL-13 induce tissue remodeling by triggering conjunctival fibroblasts to proliferate and produce collagen and vascular endothelial growth factor (VEGF), which in turn, results in papillary formation with new vessels [35]. IL-5, produced by Th2-lymphocytes and mast cells, plays a role in eosinophil activation and recruitment [36]. IL-9 is secreted by T-lymphocytes, eosinophils, and mast cells. It synergizes with IL-4 in the production of IgE and in the promotion of conjunctival tissue remodeling [31, 37, 38]. TNF-α is a multifunctional proinflammatory cytokine produced by monocytes, macrophages, DCs, mast cells, and T cells. It induces the expression of adhesion molecules on vascular endothelial cells and facilitates chemokine synthesis by immune and non-immune cells (e.g. epithelial cells) [39]. Th17 cells play a significant role in acute inflammatory response [25], since antigen-specific Th17 cells produce cytokines (IL-17A, IL-17F, IL-21, and IL-22) that trigger non-immune cells such as epithelial cells and fibroblasts to express pro-inflammatory cytokines and chemokines that induce the recruitment of immune cells such as neutrophils to the site of allergic response [29, 31]. Regulatory T cells that act to control immune responses could be either natural regulatory T cells committed to an immunoregulatory fate while still in the thymus [40] or induced variety of regulatory T cells that differentiate from naïve T cells in response to antigen [25]. Regulatory T cells via the action of immunosuppressive cytokines such as IL-10 and TGF-β are capable of downregulating the expression of B7 on DCs, which in turn, affects downstream allergen-induced activation of T cells and subsequent production of IgE [40].

2.5 Antibodies

Antibodies are immunoglobulins produced by effector B cells in response to antigenic stimulation [18, 41]. Membrane-bound immunoglobulin (mIg) or surface immunoglobulin (slg) is the antigen receptor of B cells [19]. Antibodies consist of five different types and include immunoglobulin G (IgG), IgM, IgA, IgD, and IgE. Antibodies are effector molecules that mediate humoral-mediated immune

responses, such as neutralization, opsonization, and complement activation. Th1-derived cytokines stimulate antigen-specific B cells to produce IgG-secreting plasma cells, whereas Th2-derived cytokines (e.g. IL-4 and IL-13) enhance proliferation and differentiation of antigen-specific B cells into IgE-producing plasma cells [25]. IgG is the principal antibody in serum and non-mucosal surfaces, whereas IgA is the primary antibody that participates in mucosal immune protection [42]. IgE, a major antibody that participates in type 1 hypersensitivity reactions characteristic of allergic eye diseases, binds to FCεRI found on mast cells, basophils, B cells, activated eosinophils, and follicular dendritic cells. FcεRII are present on B cells, activated T cells, monocytes, eosinophils, and follicular dendritic cells [5, 43]. Th2 cells play an important role in allergic eye diseases, since its cytokines are involved in the production of IgE, mast cell activation, and activation of eosinophils [44].

2.6 Co-stimulatory Molecules

Co-stimulatory molecules or ligands are cell surface proteins on immune cells that are involved in signal transmission. The generation of effector T cells require costimulation signals provided by interaction between costimulatory receptors and their ligands [45, 46]. CD28 is a co-stimulatory receptor on the surface of naïve T cells that binds co-stimulatory ligand B7 expressed by DCs to facilitate the activation of naïve T cells [45, 47]. It has been demonstrated that CD28/CD86 costimulatory pathway participates in production of Th2-derived cytokines that mediate eosinophil activation and production of IgE in allergic inflammation [45]. Eosinophil and Th2 cell recruitment to the site of allergic inflammation requires the action of adhesion molecules, which mediate the interaction between leukocytes and vascular endothelial cells [48].

2.7 Adhesion Molecules

Adhesion molecules are classified into three main categories: (a) the integrins, (b) the selectins, and (c) the immunoglobulin gene superfamily [48, 49]. The integrin family of adhesion molecules include lymphocyte function associated antigen-1 (LFA-1) and Very Late-activation Antigen-4 (VLA-4). LFA-1 binds to intercellular adhesion molecule -1 (ICAM-1) and ICAM-2 to form strong adhesion between leukocytes and endothelial cells on the inflamed vascular endothelium, which results in the extravasation of leukocytes [48]. The selectin family includes E-selectin, P-selectin, and L-selectin [50]. E-selectin (CD62E) is expressed on the endothelium, whereas P-selectin (CD62P) is expressed on platelets and the endothelium. E-selectin plays a role in mediating the rolling of leukocytes, such as neutrophils on the endothelium. L-selectin (CD62L) is expressed on leukocytes and it guides the

exit of leukocytes in circulation into the tissue by mediating their rolling along the vascular endothelium [49, 50]. Leukotriene B4 (LTB4), histamine, and TNF-α can activate the vascular endothelium to upregulate the expression of P-selectin and E-selectin. These selectins initiate endothelium-leukocyte interaction, that culminates in the reversible binding of leukocytes to the wall of the blood vessel [48]. ICAM-1 (CD54), ICAM-2 (CD102), vascular cell adhesion molecule-1 (VCAM-1/CD106), platelet and endothelial cell adhesion molecule-1 (PECAM-1/CD3l), and the mucosal vascular address in cell adhesion molecule 1 (MAdCAM-1) are members of the immunoglobulin gene superfamily that plays an important role in the recruitment of leukocytes such as T cells to the site of allergic inflammation [50, 51]. ICAMs on the endothelium facilitate the tight adhesion of leukocytes to the endothelium [48, 49]. TNF-α, interferon gamma (IFN-γ) and interleukin (IL)-1β can induce the expression of ICAM-1 [51], whereas TNFα can also induce the upregulation of ICAM-2 [48]. Additionally, ICAM-I is expressed on mononuclear cells, granulocytes, lymphocytes, APCs, fibroblasts, and epithelial cells. Although ICAM-1 is not expressed on normal conjunctival epithelial cells, it is upregulated on conjunctival epithelial cells following an allergic reaction, which in turn, facilitates the migration of inflammatory cells into the site of allergic inflammation [39]. Furthermore, ICAM-1 plays an important role in homing and migration of eosinophils that are involved in the inflammatory process in allergic eye disease [52]. ICAM-2 and PECAM-1 are expressed on endothelial cells and participate in adherence of leukocytes to the endothelium. PECAM-1 is also found on platelets and leukocytes [49, 50]. Vascular adhesion protein-1 (VAP-I) is an endothelial adhesion molecule. PECAM-1 and VAP-1 participate in the adhesion and transmigration of lymphocytes [50, 53]. There is an increased expression of ICAM-1, E-selectin, and VCAM-1 in allergic eye diseases [39]. It is important to note that cytokines and chemokines are capable of upregulating the expression of adhesion molecules on epithelial cells and vascular endothelium during the immunopathological process in allergic eye diseases [39] Thus, adhesion molecules are involved in mediating the three-step process involved in the allergen-induced accumulation of inflammatory cells and molecules at the site of allergic inflammation [11].

2.8 Epithelial Cells and Fibroblasts

Epithelium represents a physical barrier that protects against the intrusion of antigens through the function of tight junctions that play a vital role in the formation and maintenance of epithelial barriers [8, 54]. Epithelial cells are located at the port of entry of allergens and actively participate in allergic inflammation via the expression of cytokines, chemokines, and adhesion molecules. These expressed mediators promote the infiltration of immune cells such as eosinophils and Th2 cells to the site of allergic inflammation in the conjunctiva [39, 55, 56]. Fibroblast, a cell that produces extracellular matrix (ECM), acts as an immune modulator in allergic conditions by producing pro-inflammatory mediators in response to cytokines. Fibroblasts

in the conjunctiva and cornea in response to late phase mediators undergo increased proliferation as well as produce ECM and inflammatory mediators. In chronic allergic eye diseases, IL-4 and IL-13 can activate corneal fibroblasts to secrete eotaxin, thymus- and activation-regulated chemokine (TARC or CCL17), matrix metalloproteinase (MMP), VCAM-1, and ICAM-1. TARC is a potent chemoattractant for Th2-lymphocytes. Excessive ECM production, vascular endothelial growth factor (VEGF) secretion, and proliferation of conjunctival fibroblasts that occurs in response to IL-4 are major contributory factors to the formation of giant papillae [3, 35, 57–59]. Thus, epithelial cells and fibroblasts of the cornea and conjunctiva participate in the immunopathogenesis as well as immunopathological process that results in tissue damage and remodeling in allergic eye diseases.

2.9 Mast Cells

Mast cells, located in mucosal and epithelial tissue, are derived from mast cell progenitors that differentiate from hematopoietic stem cells under the effect of stem cell factor (SCF) [2, 60]. Additionally, IL-3 and IL-9 play a role in the growth and development of mast cells [5]. Mast cells are usually found in vascularized connective tissues in the subepithelial layer [42].There are two types of mast cells based on their location and protease content, mucosal mast cells (Tryptase-positive (MC_T) and connective tissue mast cells (tryptase and chymase-positive (MC_{TC}) with the conjunctiva containing mainly connective tissue mast cells [2, 61, 62]. Mast cells are not present in the cornea but are predominant in the conjunctiva, where they play a pivotal role in allergic eye diseases [2]. In the normal conjunctiva, the mast cells are concentrated in the conjunctival substantia propria [63–65]. In the healthy human conjunctiva, there are more than 10,000 mast cells/mm^3 located in the conjunctival stroma (substantia propria) with the number of mast cells significantly increased in chronic forms of allergic eye disease [8]. The cytoplasm of the mast cells contain up to 200 large granules with each granule containing preformed mediators such as histamine, heparin, proteases (tryptase and chymase), major basic protein, acid hydrolases, peroxidase, and phospholipases [2, 66]. Following the activation and subsequent degranulation of sensitized conjunctival mast cells, preformed mediators such as histamine and protease are released immediately followed later by the production of lipid mediators, cytokines, and chemokines. Lipid mediators include leukotrienes (LT) B4, LTC4, prostaglandin (PG) E2, PGD2, and platelet-activating factor (PAF). Cytokines released include TNF-α, IL-1α, IL-1β, IL-3, IL-4, IL-5, IL-9, IL-13, IL-25, and SCF; whereas chemokines released following activation and degranulation of mast cells include CXCL8, CCL5, CCL11, and CCL17. Growth factors include vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) [66]. These mediators along with histamine, leukotriene, and prostaglandins released following mast cell degranulation play a major role in the immunopathological process in acute and chronic forms of ocular allergy.

2.10 Histamine

Histamine, a low molecular weight vasoactive mediator stored in mast cells and basophils, is synthesized by the decarboxylation of histidine by histidine decarboxylase [67]. Its biological actions are achieved by interacting with four G-protein coupled receptors. These receptors include histamine 1 receptor (H1R), 2, 3 and 4 [68] with H1R, H2R and H4R playing a major role in allergic eye diseases [8]. H1R and H2R are expressed on immune cells (e.g. lymphocytes), non-immune cells (e.g. epithelial cells), vascular smooth muscle cells, and endothelial cells. H1R and H2R on the conjunctiva vasculature mediate vasodilation and increased vasopermeability, whereas H1R on conjunctival sensory fibers mediate ocular itch in the setting of allergic eye diseases [3, 8, 69]. H4R are expressed mainly on immune cells (mast cells, eosinophils, T cells, and DCs) [8], and as such, histamine/H4R interaction mediates recruitment of immune cells to the site of allergic inflammation in the conjunctiva resulting in exacerbation of the allergic response [8, 70]. Histamine released following mast cell degranulation affects conjunctival blood vessels, nerve endings, epithelial cells, and fibroblasts [69]. Conjunctival epithelium and fibroblasts secrete cytokines, chemokines, and adhesion molecules in response to histamine/histamine receptor interaction [71]. Thus, histamine participates in the clinical expression of the allergic response [72, 73].

2.11 Lipid Mediators

Leukotriene (LT), a potent lipid mediator synthesized via the lipoxygenase pathway of arachidonic acid metabolism, is involved in the pathological mechanism of allergic eye disease [74]. LTC4, LTD4 and LTE4 are released by degranulated mast cells and eosinophils [5, 74]. In allergic eye disease, leukotrienes have been shown to cause increased vascular leakage and increased secretion of mucus [3, 61, 75, 76]. Prostaglandin is a potent lipid mediator synthesized via the cyclooxygenase pathway of arachidonic acid metabolism [15, 64]. Prostaglandin D2 (PGD2) is produced following activation and subsequent degranulation of mast cells and it is an important mediator of ocular allergy [5, 77]. It is expressed on human eosinophils and Th2 cells. Fujishima and colleagues [77] used flow cytometry analysis to demonstrate the expression of chemoattractant receptor-homologous molecule expressed on Th2 cells and eosinophils. They were able to demonstrate that the interaction between PGD2 and CRTH2 on eosinophils resulted in PGD2-mediated recruitment of eosinophils and secretion of cytokines by Th2 cells in allergic eye diseases [77, 78]. Platelet activating factor (PAF) is a lipid mediator that plays a role in the chemotaxis of eosinophils. It is synthesized by most inflammatory cells and is involved in the pathological mechanism of allergic eye diseases [5, 79]. Okumura and colleagues [80] used liquid chromatography-tandem mass spectrometry to demonstrate the presence of PAF in patients with AC. Thus, PAF plays an important role in allergic eye diseases [80].

2.12 Chemokines

Chemokines are low molecular weight chemotactic cytokines that mediate the attraction and activation of leukocytes such as monocytes, neutrophils, lymphocytes, and other effector cells to the site of inflammation [39, 48]. CXC, CC, XC and CX3C are chemokine ligands that act on different sets of chemokine receptors. There are more than 40 chemokine ligands in humans that promote the directional migration of immune cells [81]. CCL11, produced by stromal cells and immune cells, binds to CCR3 on human eosinophils to promote their release from bone marrow and migration to the site of allergic inflammation [12]. Interleukin (IL)-8/CXCL8 is produced by immune (e.g. monocytes, macrophages) and nonimmune (e.g. fibroblasts, epithelial cells, and endothelial cells) cells. CXCR1 and CXCR2 are receptors for CXCL8 [48]. T cells, endothelial cells, and platelets secrete CCL5 that interacts with CCR1, CCR3, and CCR5 to mediate the recruitment of T cells, basophils, and eosinophils [39, 48]. Th2 cells express CCR4, CX3CR1, and CRTH2, whereas Th1 cells express CCR5 and CXCR3. These chemokine receptors and their ligands participate in Th1-type and Th2-type adaptive immune response [12, 81]. Thus, chemokines produced by activated immune and nonimmune cells play a role in allergen-induced ocular surface inflammation as well as in the recruitment of effector immune cells, such as eosinophils that contribute to the tissue remodeling and damage in the chronic forms of allergic eye diseases [82].

2.13 Eosinophils

These contain arginine-rich basic proteins and they can also secrete enzymes, IL-4, IL-6, IL-12, IL-13, CCL2, CCL11, CCL17, CXCL8, lipid mediators, eosinophil peroxidase, major basic protein, eosinophil collagenases, and matrix metalloproteinase-9. Eosinophil major basic protein is a major cause of corneal epithelial toxicity in chronic allergic eye conditions [5, 83]. Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that are expressed in physiologic and pathologic conditions [84]. They are key enzymes for breakdown of ECM associated with inflammatory reactions and wound repair [85]. Kumagai and colleagues demonstrated that active forms of MMP-2 and MMP-9 are significantly raised in patients with allergic eye disease, and as such, these active forms of MMP are responsible for the inflammatory reactions and tissue remodeling in the ocular surface of these patients [86, 87]. Eosinophils in the non-active state do not express surface markers but when activated by cytokines and chemokines, they upregulate the expression of FcεRI, major histocompatibility class II molecules, CD86, and CD40, and as such, they are capable of presenting antigens to activated $CD4^{+}$T cells [83, 88]. The recruitment of eosinophils is associated with their infiltration of the conjunctiva of patients with allergic eye diseases [39, 89, 90].

2.14 Neutrophils

Neutrophils are important innate effector immune cells that act as phagocytes. These short-lived immune cells secrete prostaglandin, leukotriene, IL-1β, TNF-α, MMP-9, neutrophil elastase, and myeloperoxidase [15, 32, 48, 91]. Neutrophils are the most abundant immune cells in innate immunity that participate in acute inflammatory reactions and it has been shown to be increased in patients with chronic forms of allergic eye diseases, such as vernal keratoconjunctivitis and atopic keratoconjunctivitis [19, 92, 93].

3 Biology of the Ocular Surface

The anatomy, physiology, and immunology of the conjunctiva, limbus and cornea will be discussed, since the conjunctiva, cornea and limbus are ocular structures affected by allergic inflammation. The epithelium of these structures forms a physical barrier that prevents foreign substances such as allergens from gaining access to the subepithelial tissues [94, 95].

3.1 Structure and Function of the Ocular Surface

The conjunctiva is a highly vascularized, immunologically active mucosal tissue; however, there are several regulatory mechanisms in place to control the immune response in order to prevent tissue damage [96]. The conjunctiva consists of an epithelium and stromal layer. The epithelium of the conjunctiva is a non-keratinized mucous membrane that houses goblet cells and intraepithelial leukocytes. The epithelial cells are held together by tight junctions. The conjunctival stroma consists of collagen, fibroblasts, vasculature, lymphocytes, macrophages, DCs, and mast cells. It is noteworthy that eosinophils are not present in the healthy conjunctiva [39, 97, 98]. The limbus is an annulus of tissue, which acts as a junctional barrier that separates the cornea from the conjunctiva. It consists of a vascular network of palisades of Vogt that contain stem cells and Langerhans' cells. It is noteworthy that the removal of damaged epithelial cells via constant shedding of the superficial epithelial cells and their replacement by stem cells contribute to the ocular surface's immune protection [97, 99–102]. As such, the limbus contributes to the immune-surveillance of the ocular surface [15, 103]. The cornea consists of the epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium. The corneal epithelium consists of Langerhans' cells, superficial cells, wing cells, and basal cells. The corneal stroma constitutes 90% of the entire corneal thickness and it consists of macrophages, collagen, fibroblasts, and immature DCs in the peripheral cornea. Corneal APCs exist in the immature immunological state and they include

Langerhans' cells and DCs. Langerhans' cells express MHC-II$^-$, CD80$^-$, and CD86$^-$ while dendritic cells express CD45$^+$, CD11b$^+$, CD11c$^+$, DC-SIGN$^-$, MHC-II$^-$, CD80$^-$, and CD86$^-$. Macrophages in the cornea express CD45$^+$, CD11b$^+$, CD11c$^-$, HLA-DR$^-$, F4/80$^+$, and DC-SIGN$^-$. Following a breach in the corneal epithelial barrier, CD45$^+$ CD11b$^+$ CD11c$^-$ macrophages located in the posterior stroma of the cornea provides an initial defense against foreign substances by producing cytokines and chemokines that participate in the innate immune response [23, 104]. Sensory nerve fibers derived from the ophthalmic division of the trigeminal nerve supply to the cornea and the vasoactive intestinal peptide (VIP) secreted by theses nerves contributes to immune regulation via increasing production of immunoregulatory cytokines and blocking the expression of pro-inflammatory cytokines [21, 96]. Corneal epithelial cells are joined together by a tight junction complex that links the cytoskeletons of adjacent epithelial cells, and as such, the tight junction contributes to the physiological barrier function of the epithelium via blockade of access of allergens to immune cells in the sub-epithelial layer [8, 54, 105, 106].

3.2 Immunology of the Ocular Surface

The epithelium of the ocular surface utilizes effector mechanisms of both arms of the immune system to provide immune surveillance and immunoregulation [107–109]. Conjunctival-associated lymphoid tissue (CALT) is a component of the Eye-associated lymphoid tissue (EALT). CALT is an ocular surface immune protection system that consists of diffuse lymphoid effector tissue and conjunctival lymphoid follicles (CLF). It maintains balance between immune tolerance and inflammation, which is tilted toward immune tolerance via the action of regulatory T cells and immunosuppressive cytokines. Diffuse lymphoid effector tissue, an efferent arm of the CALT, consists of DCs, mast cells, macrophages, IgA-secreting plasma cells, and intraepithelial and lamina propria effector T cells. Conjunctival lymphoid follicles, an afferent arm of the EALT, are interspersed within the diffuse lymphoid effector tissue. CLF consists of B cells, parafollicular T cells associated with lymph vessels and high endothelial venules (HEV), and apical follicle-associated epithelium (FAE) with M cells for antigen transport. Thus, CALT provides immunosurveillance for the ocular surface through its ability to detect antigens and generate effector immune cells in response to invasion of the ocular surface [3, 98, 108, 110]. Afferent and efferent immunoregulatory mechanisms of the ocular surface involve the action of mediators and cells of the immune system. The afferent immunoregulatory mechanisms include controlling maturation of DCs, controlling production of pro-inflammatory cytokines by epithelium and DCs via TLR-mediated activation pathways, and reducing expression of cell adhesion molecules by vascular endothelial cells. The efferent immunoregulatory mechanism is mediated by regulatory T cells and immunosuppressive or immunoregulatory cytokines [96]. Langerhans' cells, DCs and macrophages in the conjunctiva and cornea are the main APCs of the ocular surface that participate in the innate immune surveillance system. They constitute the first line of defense of the ocular surface to foreign sub-

stance when the physicochemical barrier is breached [111]. Regulatory T cells inhibit effector $CD4^+$T cell-mediated ocular surface inflammation whereas immunoregulatory cytokines (e.g. IL-10 and TGF-β) direct DCs to promote differentiation of naïve $CD4^+$T cells into regulatory T cells. Additionally, TGF-β inhibits proliferation of damaged epithelial cells [21, 96, 112]. Tear film provides a physicochemical barrier that prevents adherence of allergens to the epithelium of the conjunctiva via flushing and diluting these allergens in the tear film [108]. Complement system consists of plasma and membrane-bound protein and plays an important role in innate immune surveillance. It consists of proteins that initiate and activate the complement pathway and complement proteins that regulate complement activities. Decay activating factor (DAF, CD50), membrane cofactor protein (MCP, CD46), complement receptor 1 (CR1, CD35), and membrane inhibitor of reactive lysis (MIRL, CD59) are complement regulatory proteins that block various complement functions at different stages of the complement cascade [113]. Expression of complement regulatory proteins such as DAF and CD59 by epithelial cells of the ocular surface protect the cornea from complement-mediated inflammation and cytolysis respectively [48, 114, 115]. Furthermore, Fas ligand (FasL; CD95L) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expressed on the epithelium mediates immunoregulatory processes by preventing immune-mediated inflammation through the induction of apoptosis of infiltrating immune cells that express the receptor for FasL (Fas; CD95) and TRAIL [96, 115]. Deregulation of resident lymphocytes of CALT results in ocular surface inflammation, as pro-inflammatory cytokines can activate epithelial cells of the ocular surface to express adhesion molecules, proteases, co-stimulatory molecules, and MHC class II molecules. The expression of costimulatory molecules and MHC class II on epithelial cells facilitate their interaction with $CD4^+$ T cells. Additionally, increased levels of proteases such as MMPs, can cause a breach of the epithelial physical barrier, which allows allergens access to immune cells in the subepithelial layer [21, 98]. Thus, deregulation of the CALT results in immune-mediated ocular surface inflammation [108, 110]. The cornea is an immunologically privileged tissue, and corneal immune privilege status maintains homeostasis and prevents the cornea from immune mediated damage. Although cornea is an immune privileged tissue, it does contain immune cells, such as DCs and macrophages in the immature state [23]. Corneal immune privilege status is attributed to lack of corneal vasculature and lymphatics and absence of mature DCs in the cornea. Additionally, the lack of TLRs on the apical layer of the corneal epithelium provides an immunosilent environment for the epithelium, and contribute to corneal immune privilege status; however, TLR-mediated innate immune response can occur when the corneal epithelial barrier is breached [21, 22, 115, 116]. The lack of MHC classII molecules in the healthy cornea constitutes part of the cornea's immune privilege status. Antigen presentation to T cells by immature DCs leads to the generation of anergic T cells and subsequent induction of immune tolerance, and this protects the cornea from T cell-mediated ocular surface damage [23]. The cornea and conjunctiva are located at the port of entry for allergens, and their epithelial cells, APCs, and fibroblasts participate in immune mechanism by secreting inflammatory mediators during allergic inflammation [39].

4 Immunopathology of Allergic Eye Disease

This section will discuss the immunopathogenesis and immunopathology of the major types of allergic eye disease. Allergic conjunctivitis is an ocular surface disease characterized by IgE-mediated mast cell degranulation, and sensitization, early phase, and late phase of the allergic immune response involved in the pathological mechanism will be discussed. Additionally, the pathological mechanisms of GPC as part immunologic and part mechanical involving the actions of Th2 cells will be discussed. The immunopathogenesis and immunopathology of AKC is multifactorial involving chronic IgE-mediated mast cell degranulation and T cell-mediated immune mechanisms. The immunopathogenesis and immunopathology of VKC is multifactorial involving Th2 cells and Th2-derived cytokines, chemokines, adhesion molecules and inflammatory enzymes. Beside these, the immunopathology along with clinical correlates of allergic eye disease, therapy and clinical outcomes will be discussed.

4.1 Allergic Conjunctivitis

AC is a bilateral inflammatory process that involves the conjunctiva [117]. It is the most prevalent form of allergic eye disease that causes clinical manifestations when IgE bound to sensitized mast cells are cross-linked by allergen. AC constitutes over 90% of all forms of allergic eye disease, and it has a seasonal variant (seasonal AC) due to outdoor allergens and perennial variant (perennial AC) due to indoor allergens [18, 118]. Tree pollen and grass pollen are associated with seasonal AC whereas pet dander and dust mite are associated with perennial AC [119, 120]. Environmental allergens such as pollen, mold and dust mite secrete proteolytic enzymes that promote allergenicity of the allergen and disrupt the barrier function of the ocular surface. Itching, conjunctival hyperemia, chemosis, mucoid discharge, tearing, burning and eyelid swelling are hallmark features of AC [5–8]. In this condition, histamine, leukotrienes, cytokines, chemokines, proteases and prostaglandins produced by activated mast cells play a crucial role in conjunctival inflammation associated with AC [4, 121].

4.1.1 Immunopathogenesis and Immunopathology

The immune mechanism of AC occurs in three phases following exposure of the conjunctiva to allergens. In the sensitization phase, allergens are able to gain access to immune cells in the subepithelial layer via the action of their protease activating protease-activated receptor-2 (PAR-2) in the conjunctiva and the subsequent degradation of the tight junction between epithelial cells [122]. DCs in their immature state will engulf and process these allergens resulting in maturation of DCs with

upregulation of MHC class II molecules, CD80, and CD86. The processed allergen is displayed on the mature DC as a peptide complex to MHC class II molecule. Mature DC with peptide-MHC class II complex migrate to the regional lymph node where they interact with naïve T cells resulting in the activation of T cells and their subsequent proliferation and differentiation into Th2 cells. IL-4 and IL-5 are important cytokines released by allergen-specific Th2 cells. IL-4 induces the proliferation and differentiation of allergen-specific B cells into IgE producing plasma cells, which is preceded by T cell-dependent B cell activation involving peptide-MHC class II complex on BCR and CD40 on allergen-specific B cells interacting with TCR and CD40L on T cells respectively [3, 123]. Allergen-specific IgE binds via their Fc region to Ig-like domain of alpha chain of FcεRI located on the surface of mast cells in the conjunctiva leading to the induction of mast cell sensitization. Primed mast cells participate in type I hypersensitivity immune reaction that are characteristic of AC [2, 3, 124, 125]. Additionally, TSLPs play a role in generating IgE-producing plasma cells. Allergens in contact with epithelial cells of the conjunctiva, induce these cells to produce TSLP that interact with TSLP receptors on DCs. TSLP-activated DCs induce naïve T cells to differentiate into Th2 cells that produce IL-4 that induce allergen specific B cells to undergo proliferation and differentiation into IgE-secreting plasma cells. Thus, conjunctival epithelial cells via the action of TSLP participate in the initiation of the sensitization phase of AC. The binding of these allergen-specific IgE to FcεRI on mast cells completes the process of mast cell priming (Fig. 1) [3, 10, 11, 18, 123, 125]. The elicitation or activation phase of AC occurs when previously sensitized eyes are exposed to allergens, culminating in multivalent allergen binding and inducing crosslinking of IgE-FcεRI complex on sensitized mast cells in the conjunctiva. Crosslinking leads to activation and subsequent degranulation of primed mast cells and release of histamine, which is followed by the synthesis of lipid mediators and cytokines (Fig. 2) [3, 120, 123, 126, 127]. Additionally, chemokines and adhesion molecules are released by degranulated mast cells. When histamine bind to their receptors on the conjunctival epithelium, it results the in disruption of the barrier function of the conjunctival epithelium as well as activation of conjunctival epithelial cells with subsequent release of adhesion molecules, chemokines, and pro-inflammatory cytokines. The clinical manifestations of the early phase of the allergic reaction, such as itching, edema, hyperemia, and tearing are attributed to the action of histamine on vascular endothelium, sensory nerve fibers, immune cells, and conjunctival epithelium [120, 123, 127–131]. Additionally, tryptase is also released and it induces proliferation of fibroblasts in the conjunctiva. It is of note that histamine and tryptase are biomarkers of IgE-mediated allergic reaction in AC [3, 120]. The late phase of AC is mediated by prostaglandins, leukotrienes, and cytokines. Prostaglandin induces vasodilation and intensifies the histamine-mediated ocular pruritus, whereas leukotrienes induce vasodilation and increased vascular permeability [123]. Degranulated mast cells release cytokines such as IL-4, IL-5, IL-13, and TNF-α as well as chemokines such as CXCL8, CCL3, CCL5, CCL11, and CCL17. Cytokines play a crucial role in the activation of immune cells such as eosinophils, lymphocytes, and neutrophils. Chemokines recruit eosinophils and other immune cells to the site of

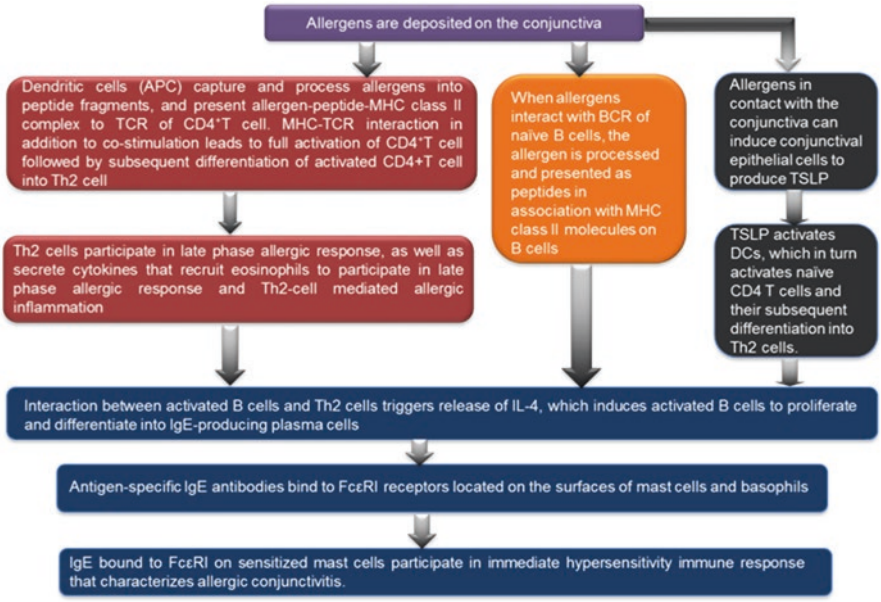

Fig. 1 Sensitization phase of allergic immune response that involves allergens interacting with DC, B cells and conjunctival epithelial cells, and subsequent interaction between DCs and $CD4^{+}$T cells that leads to the generation of Th2 cells

allergen-induced inflammation in the conjunctiva [60, 66, 121]. Vasodilation mediated by leukotrienes, prostaglandins, and histamine causes conjunctival hyperemia, whereas vascular permeability mediated by histamine and leukotrienes results in an influx of fluid from leaky conjunctival vessels into the mucosal tissue causing conjunctival edema or chemosis [118, 120, 123]. Cytokine and chemokines mediate cellular infiltration of the conjunctiva, in which inflammatory cells and mediators released by recruited inflammatory cells exacerbate the conjunctival inflammation in AC. Conjunctival fibroproliferative lesions seen in AC is attributed to the action of recruited immune cells to inflamed conjunctiva. Lipid mediators play a major role in the early stages of late phases of AC whereas cytokine and chemokines are involved in sustaining the inflammation in the late phase [3, 18, 118, 123, 132].

4.1.2 Diagnosis, Management, and Prognosis

Diagnosis of AC is mainly clinical with skin prick testing or radioallergosorbent test (RAST) used for confirmatory diagnosis and identification of the offending agent [117]. Consulting with an allergist to assist in identifying the causative agents may be beneficial. Avoidance of the offending environmental allergen by staying indoors, wearing a filter mask when outdoors, avoiding freshly cut grass constitutes the first line therapy of AC. Saline irrigation, avoidance of eye rubbing, and palliative therapy

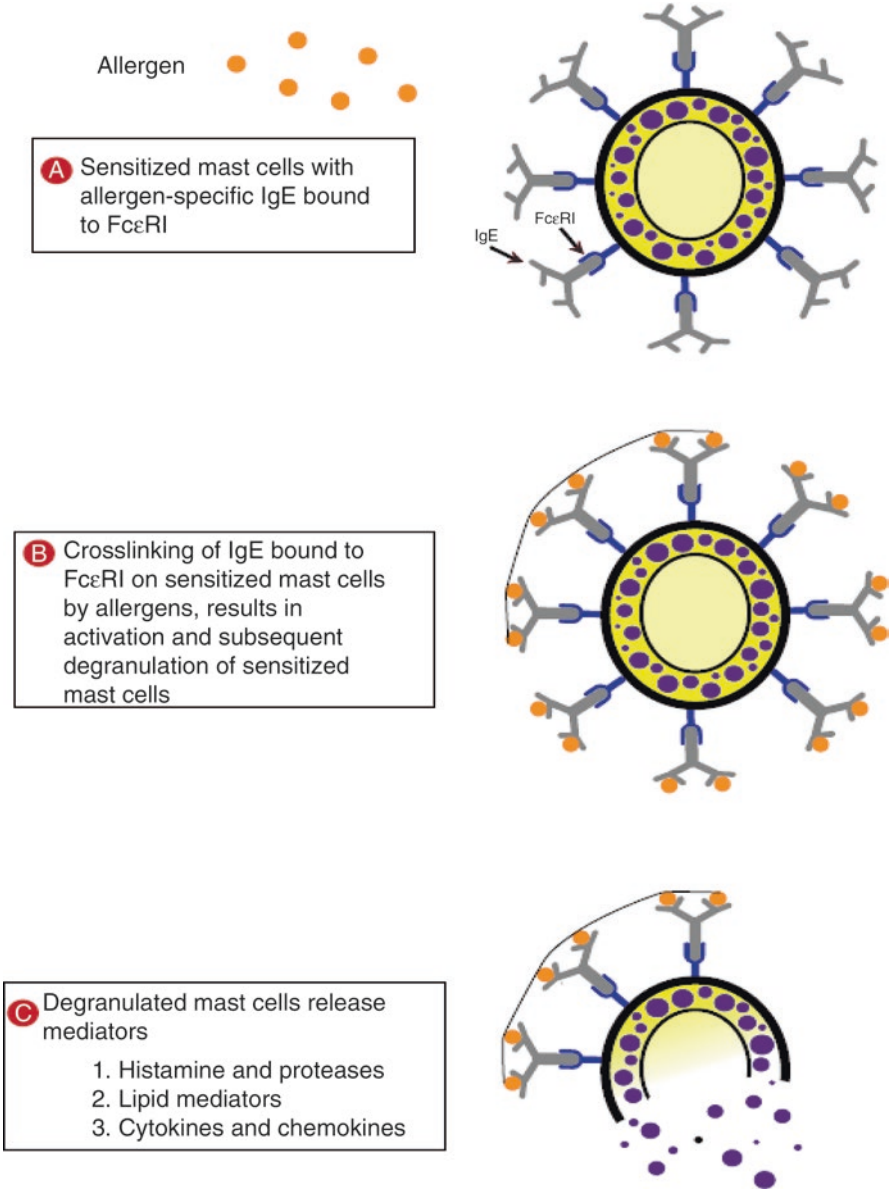

Fig. 2 Early phase allergic response occurs when crosslinking of IgE-FcεRI complex on primed mast cells leads to activation and subsequent degranulation of conjunctival mast cells and release of histamine, lipid mediators and cytokines

with cool compress are non-pharmacological management modalities that are beneficial for patients with AC. The application or administration of refrigerated preservative-free ocular lubricants in conjunction with cool compresses can induce vasoconstriction, which in turn can counteract the allergen-induced vasodilation effect associated with conjunctival hyperemia. Furthermore, preservative-free ocular lubricant can dilute and flush away environmental allergens and possibly other inflammatory mediators on the ocular surface without having any impact on the activity of histamine, tryptase, and other inflammatory mediators [117, 132]. Oral antihistamines play a role in the pharmacotherapy of AC via reduction of allergic sensitivity. Topical ophthalmic pharmaceuticals such as antihistamine, non-steroidal anti-inflammatory agents, corticosteroids, mast cell stabilizers, and antihistamine/mast cell stabilizer combination are used for treating patients with AC [124]. Majority of cases respond to antihistamine or topical antihistamine/mast cell stabilizer combination; however, an individual presenting with hyperacute expression of AC, severe AC, or recalcitrant AC would benefit from mast cell stabilizer or antihistamine/mast cell stabilizer combination and pulse topical steroidal therapy along with a tapering schedule. Anti-allergic nasal sprays such as azelastine hydrochloride nasal spray or oral antihistamine along with topical antihistamine/mast cell stabilizer combination ophthalmic agents would be beneficial for individuals who have allergic rhinoconjunctivitis. It is of note that oral antihistamines can reduce the aqueous component of the tear film; however, they usually have a long duration of therapeutic effect with delayed onset of action. As such, it is recommended that clinicians should prescribe topical antihistamine or antihistamine/mast cell stabilizer combination ophthalmic agents with rapid onset of action and more than 8 hours of therapeutic effect. The antihistamine in topical antihistamine/mast cell stabilizer combination ophthalmic agents provide an immediate therapeutic resolution of histamine-induced allergic expression, whereas the mast cell stabilizer provides long term anti-allergic prophylaxis [133–135]. AC has a favorable prognosis but tends to reoccur. However, untreated AC is associated with disruption of barrier function of the conjunctival epithelium, which results in persistent activation and degranulation of primed conjunctival mast cells [117, 136].

4.2 Giant Papillary Conjunctivitis

Giant papillary conjunctivitis (GPC) is not strictly an allergic disease, but an inflammatory condition characterized by papillary hypertrophy of the superior tarsal conjunctiva with little or no corneal involvement [45, 137]. It may be due to persistent mechanical ocular surface irritation or microtrauma from contact lens, ocular prostheses, exposed sutures after ocular surgery, or elevated corneal deposits. Additionally, hypersensitivity reaction to antigenic material derived from protein deposits on contact lens or ocular prosthesis [45, 138–141]. This section on GPC will focus on contact lens induced papillary conjunctivitis (CLPC) or contact lens induced GPC. CLPC may result from an immune-mediated hypersensitivity response to protein deposits on the contact lens surface and/or ocular surface irritation due to damaged contact lens,

poorly fitted contact lens, and/or irregular contact lens edge [137, 142]. CLPC may affect both atopic and non-atopic individuals with no gender or age predilection [138, 139]. CLPC occurs earlier in individuals wearing silicone soft hydrogel contact lenses than in individuals wearing rigid contact lenses. However, individuals wearing silicone soft hydrogel contact lenses are more susceptible to developing CLPC than individuals wearing soft hydrogels [61, 141, 143]. It is of note that CLPC is more likely to occur in patients wearing contact lenses made of ionic material compared to those wearing contact lenses made of non-ionic material [144].

4.2.1 Immunopathogenesis and Immunopathology

CLPC is a multifactorial ocular surface inflammation with a pathogenesis that is partly immunologic and partly mechanical. The immunologic aspect of the pathogenesis of CLPC occurs when proteinaceous deposits on a contact lens surface becomes antigenic, which results in the generation of antigenic-specific Th2-mediated immune response. Th2 cells provide signals to activated B cells to produce IgE-secreting plasma cells [145]. Additionally, the activation of complement leads to the generation of complement mediators of inflammation (C3a and C5a) that act on vascular endothelium to upregulate the expression of adhesion molecules and also acts on mast cells to induce their activation and degranulation, and subsequent release of pro-allergic (e.g. histamine) and pro-inflammatory (e.g. cytokines and chemokines) mediators [48, 91, 141]. Szczotka and colleagues [146] demonstrated that tear levels of DAF were significantly reduced in individuals with CLPC, and as such, the reduced levels of DAF allows for the activation of complement and subsequent generation of complement mediators of inflammation. C5a can upregulate the expression of adhesion molecules on vascular endothelium leading to vasodilation and vascular permeability. Because mast cells express receptors for C3a and C5a, these complement mediators of inflammation can induce the chemotaxis and activation of conjunctival mast cells [147]. As such, interactions between complement mediators of inflammation and their respective receptors on mast cells are likely to be involved in the immunopathology of CLPC. The mechanical aspect of the pathogenesis of CLPC involves the generation of proinflammatory cytokines in response to mechanical trauma or irritation of the conjunctiva. IL-8 released by traumatized conjunctival epithelial cells attracts neutrophils to the site of inflammation. Because both IL-1 and TNF-α released by the damaged epithelial cells can induce both epithelial and vascular endothelial cells to secrete chemokines and adhesion molecules respectively, they plays a role in recruitment of immune cells to the site of conjunctival inflammation [39, 61]. Furthermore, C5a-C5a receptor interaction on monocytes and neutrophils induces their recruitment to the site of traumatized conjunctiva [147]. Thus, interaction of complement mediators of inflammation and IgE with mast cells triggers the release of pro-inflammatory mediators. The presence of IgE and IL-8 in the tears of individuals with CLPC is suggestive of immune-mediated and mechanical-induced CLPC respectively [39, 61]. This is supportive of the multifactorial nature of the pathogenesis of CLPC. Histopathological examination of con-

junctiva in patients with CLPC reveals infiltration with lymphocytes, neutrophils, and eosinophils. Although, eosinophils are present in the conjunctiva of patients with CLPC, it has little/no role in the immunopathology of CLPC, since the levels of eotaxin and eosinophil cationic protein (ECP) are not significantly increased in these patients with GPC [45, 138, 148]. Patients with CLPC have significantly less eosinophils and eosinophil major basic protein (EMBP) than patients with VKC [138, 140]. Thus, the immunologic component of the pathogenesis of CLPC is due to increased levels of IgE, chemokines, cytokines, $CD4^+$T cells, and complement mediators of inflammation [141]. The normal tarsal conjunctiva has a satin appearance and it is a pink mucous membrane with fine vessels radiating perpendicular to the tarsal margin [141]. The symptoms of CLPC include contact lens awareness, itching, excessive contact lens movement, decreased contact lens tolerance, and blurred vision from coatings on the contact lens surface [138, 140, 144]. There is little/no obscuration of normal conjunctival vascular pattern in the mild form of CLPC. However, there is significant obscuration of normal conjunctival vascular pattern in moderate and severe forms of CLPC. Patients with CLPC present with subconjunctival scarring, fibrosis of the apices of papillae, papillary hypertrophy, and hyperemia of tarsal conjunctiva (Fig. 3) [141]. In severe giant papillary conjunctivitis, the papillae on the upper tarsal conjunctiva are large (1 mm or larger) with flattened, scarred apices that stain positively with sodium fluorescein [138, 141].

4.2.2 Diagnosis, Management, and Prognosis

The presence of papillae (0.3 mm in diameter or larger) on the superior palpebral conjunctiva induced by immune response to antigens and/or mechanical irritation from contact lenses is diagnostic of CLPC [139, 149]. The goal of management of CLPC is to remove the trigger factors via discontinuation of contact lens wear until the inflammatory reaction subsides and the patient becomes asymptom-

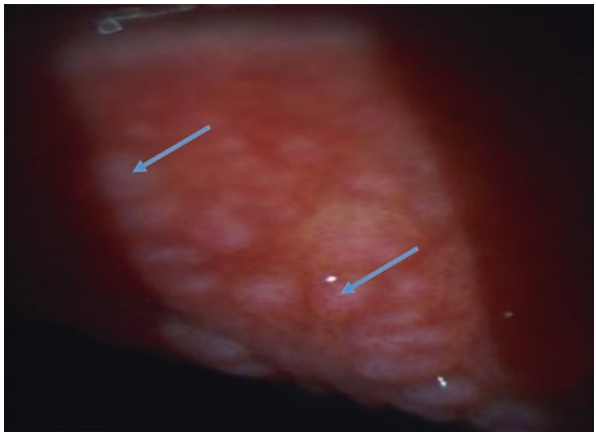

Fig. 3 Giant papillae on the superior palpebral conjunctiva in a patient with CLPC (blue arrow)

atic. When this is achieved, contact lens wear could be resumed with therapeutic intervention that does not interfere with contact lens wear. Anti-allergic and anti-inflammatory therapies would be necessary to control the ocular hypersensitivity and inflammatory cascade in CLPC [61, 138]. An important aspect of contact lens hygiene is to keep contact lens deposition to a minimum via weekly enzymatic contact lens cleaning. Maintaining a resolved state of CLPC would entail refitting the patient with new contact lens either in the same or different material and design, decreasing contact lens wear time, regularly replacing contact lenses, and instituting regular contact lens cleaning and disinfection [140, 144]. It is important to educate the patient of not resuming contact wear lens until inflammatory reaction, corneal epithelial defect and apical staining of the conjunctival papillae are completely resolved. Patients who do not respond to conventional therapy require short-term topical therapy [150]. Bartlett and colleagues [137] demonstrated the efficacy of loteprednol etabonate in treating CLPC. Kymionis and associates [151] reported success with using topical tacrolimus 0.03% ointment to treat severe GPC that was unresponsive to conventional therapy. Non-pharmacological management strategies are usually effective in CLPC; however, pharmacological therapy would become necessary when CLPC does not respond to non-pharmacological management strategies. Maintenance pharmacologic therapy may involve the use of once-daily or twice-daily dosed anti-allergic medication on a long term basis, which could be started prior to the allergy season if the patient has a history of atopy [132]. The long-term prognosis of a patient with CLPC is mostly good; however, ocular complications due to chronic inflammation or treatment side effects may ensue [151]. Although the prognosis is typically good for cases that require non-pharmacologic and pharmacologic intervention, prevention is the best strategy.

4.3 Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is a sight-threatening, chronic inflammatory disease of the ocular surface and periocular tissue. It is characterized by chronic conjunctivitis, progressive infiltration of the cornea, and corneal vascularization and fibrosis [117, 152–154]. It is associated with atopic dermatitis and other allergic conditions. It is the most severe form of chronic ocular surface allergy with a great potential to cause ocular surface complications and damage [153, 155]. AKC is more common in men and it usually begins in late teens or early twenties with the clinical course of the disease persisting until the fourth or fifth decade of life [156, 157]. Patients with AKC have an inherited predisposition to atopy with a positive family history of allergic disorders such as asthma. The systemic disorders associated with AKC include hay fever, bronchial asthma, atopic dermatitis, food allergies, urticaria and nonhereditary angioedema [157].

4.3.1 Immunopathogenesis and Immunopathology

AKC has a multifactorial pathogenesis with T cells, cytokines, hormonal factors, genetic factors, and conjunctival hyperreactivity having an impact on the pathogenesis [45]. The immunopathology of AKC involves chronic IgE-mediated mast cell activation, T cell-mediated inflammation, T cell-derived cytokines, eosinophils, basophils, and other inflammatory cells [124, 158]. The histopathological finding in the conjunctiva of patients with AKC reveals elevated levels of T cell-derived cytokines, significant levels of toxic mediators released from degranulated eosinophils and neutrophils, increased goblet cell proliferation, presence of regulated on activation, normal T cell expressed and secreted (RANTES) and ICAM-1, and high levels of IgE in tears [45, 156, 159, 160]. Thus, the damage to the ocular surface in AKC is due to chronic expression of pro-allergic mediators, inflammatory mediators, and infiltration of effector cells [161, 162]. Patients with AKC usually present with papillary hypertrophy of the lower palpebral conjunctiva, eyelid edema, limbal gelatinous hyperplasia, chemosis, conjunctival hyperemia, stringy discharge, chronic ocular itch, meibomian gland dysfunction, and corneal epithelial defects [117, 156, 157, 163]. In moderate to severe forms of AKC, there is conjunctival subepithelial fibrosis, fornix foreshortening, and persistent corneal epithelial defects [164]. The decrease in mucin 5AC (MUC5AC) levels are usually associated with conjunctiva squamous metaplasia, tear film instability, and significant reduction in goblet cell density. Tear film instability in AKC is due to meibomian gland dysfunction that causes alteration in the composition of tear film lipids [45, 165]. Eyelid and periorbital involvement in AKC are seen as hyperpigmentation of the periorbital skin, keratinization of the eyelid margin, trichiasis, eyelid edema, and eczema of the periocular skin [154, 157, 166]. Conjunctival manifestations in AKC include papillary hypertrophy of the inferior palpebral conjunctiva, conjunctival subepithelial fibrosis, fornix foreshortening, and conjunctival chemosis and hyperemia. Limbal involvement in AKC includes perilimbal gelatinous hyperplasia and limbal hyperemia [154, 164, 166]. Corneal involvement is usually secondary to effects of inflammatory mediators on the ocular surface and tear film, and these corneal signs include persistent corneal defects, filamentary keratitis, corneal ulceration, peripheral micropannus, corneal neovascularization, and pseudogerontoxon [52, 154, 156, 157, 166]. The crystalline lens opacification in AKC is predominantly anterior subcapsular cataract that may progress into complete lenticular opacification [156, 167].

4.3.2 Diagnosis, Management and Prognosis

Diagnosis is based on clinical manifestations indicative of AKC with a skin prick test or a RAST to identify the allergen-specific IgE [117]. The goal of management in AKC is to eliminate or avoid the offending agent, control ocular surface inflammation, reduce exacerbations, and prevent ocular surface and periocular tissue damage. Because AKC is a chronic ocular surface inflammatory disease, anti-allergic and anti-inflammatory pharmacotherapy in addition to supportive therapy are nec-

essary. Supportive therapy in allergic eye disease involves avoidance of inciting agents, cool compress application, and ocular surface lubrication with preservative-free ocular lubricants [52, 157, 166, 168, 169]. Steroidal therapy is necessary and it should be used with caution due to the increased risk of infection, cataract, corneal melting, and elevated intraocular pressure [157]. There are therapeutic benefits of using systemic cyclosporine in treating AKC that is refractory to conventional therapy [152]. Nivenius and colleagues [170] demonstrated the therapeutic potential of tacrolimus as a suitable alternative to topical steroidal therapy for treating periocular eczema; however, during therapy with tacrolimus, the patient should avoid ultraviolet exposure. García and colleagues [171] demonstrated the therapeutic potential of tacrolimus 0.03% dermatologic ointment for treating AKC that is unresponsive to conventional treatment. AKC is a chronic, immune-mediated ocular surface disease that has the potential to cause ocular surface and periocular tissue damage if left untreated. Complications of AKC include subepithelial fibrosis, decreased tear production, lid margin keratinization and malposition, fornix foreshortening, symblepharon formation, corneal neovascularization and corneal ulceration [153, 162, 169]. The corneal lesion in AKC may be multifactorial with a mechanical component associated with trauma to corneal epithelium by giant papillae and inflammatory component due to inflammatory mediators released by eosinophils, T cells, basophils, and/or mast cells [172]. Thus, without prompt and appropriate management, it will progress to a potentially sight-threatening sequelae.

4.4 Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is a multifactorial ocular surface inflammatory condition that is associated with genetic, immune, and environmental factors [173]. It is predominantly a Th2 cell-mediated chronic inflammatory disease with nonspecific hypersensitivity responses characterized by conjunctival fibroproliferative lesions such as giant papillae of the superior palpebral conjunctiva and/or gelatinous limbal papillary hyperplasia, as well as itching, limbal infiltration, conjunctival hyperemia, and corneal involvement [174–176]. VKC affects mainly children and young adults with preponderance in males [85, 177]. The three forms of VKC based on the main site of papillary reaction include limbal, mixed, and palpebral VKC [119, 178, 179]. The tarsal form of VKC is characterized by the presence of papillary hypertrophy that over time may assume a cobblestone appearance on the upper palpebral conjunctiva. This form is common in temperate regions, and vernal ulcers and plaques are usually a common complication [82, 86]. Gelatinous limbal papillary hyperplasia is a hallmark feature of the limbal form of VKC [180]. Although VKC usually resolves within 4–10 years after onset, it could progress to atopic keratoconjunctivitis in the late teens and early twenties [82, 119, 177, 181]. The perennial variant of VKC is common in warm climates while the seasonal variant is usually common in temperate region with flare ups occurring in the spring and summer [177]. However, this variation in presentation is dependent on the allergic disposition of the patient and climate [119]. Approximately 50% of patients

with VKC have a positive family history of atopy, which confirms that non-IgE-mediated mechanisms are involved in the immunopathology of VKC [76, 181, 182].

4.4.1 Immunopathogenesis and Immunopathology

VKC is predominantly a Th2 cell-mediated allergic inflammatory disease characterized by over expression of Th2-derived cytokines, chemokines, adhesion molecules, histamine, eosinophils, growth factors, enzymes, mast cells, macrophages, and dendritic cells [68, 82, 85]. Mast cells and Th2 cells in the conjunctiva of allergic eye disease release IL-4, IL-5 and IL-13 that play a pivotal role in the immunopathology of VKC [39, 183–185]. TNF-α is also released by degranulated conjunctival mast cells [184, 185]. Because there is an increased level of dendritic cells in the cornea and conjunctiva in VKC, dendritic cells play a predominant role in the immunopathogenesis of VKC [186]. Climatic, environmental, hormonal, genetic, and neural factors may influence the pathogenesis of VKC [178, 187, 188]. The involvement of neural factors in the pathogenesis of VKC is demonstrated by the overexpression of nerve growth factor (NGF) in serum and NGF receptors on the conjunctiva. Hormonal factors are characterized by the overexpression of estrogen and progesterone receptors on the conjunctiva, suggestive of a potential role of sex hormone in VKC pathogenesis [76, 187, 189]. Estrogen and androgen exert immune-enhancing and immunosuppressive effects on the humoral and cellular immune response respectively. As such, androgen could be considered a natural anti-inflammatory hormone. It has been hypothesized that recovery of VKC at puberty or spontaneous remission of VKC in late puberty could be due to the immunosuppressive and protective function of androgen. The effect of these steroid hormones may explain the difference in the course of VKC in males and females [57]. Tears of patients with VKC have significantly increased levels of hemopexin, a type II acute phase reactant glycoprotein upregulated by IL-6. Hemopexin has serine protease and pro-inflammatory activity, and as such, it may have a role in tissue remodeling in VKC [190]. Hemopexin possess antioxidant properties, and increased levels of hemopexin correlate with pathological changes in the cornea, conjunctiva, and limbus [191]. Abelson and associates [192] demonstrated high levels of histamine in tears and attributed this to a defect in histaminase. This increased tear level of histamine and its effects on the ocular surface could be exacerbated by effects of chronic eye rubbing [82]. Allergic inflammatory mediators such as histamine can trigger the epithelium of the ocular surface to express ICAM-1, cytokines, and chemokines [193]. Chemokines expressed by activated epithelial cells participate in the recruitment of immune cells such as T cells, neutrophils, and eosinophils to the ocular surface perpetuating and exacerbating inflammatory reaction at the site of allergic inflammation [184, 193]. The expression of MMPs by these activated epithelial cells can facilitate the access of inflammatory mediators into the subepithelial tissue via degradation of the ECM and cell-to-cell junctions [193]. Fibroblasts in the conjunctiva and cornea are involved in formation of giant tarsal papillae and gelatinous limbal thickening. It also exacerbates and perpetuates the allergic process via the release of cytokines, chemokines, and adhesion molecules such as VCAM-1 [194]. During allergic inflammation, corneal

fibroblasts express CCL17, eotaxin, ICAM-1, and VCAM-1, which promotes the recruitment and infiltration of eosinophils and other immune cells. Thus, corneal and conjunctival fibroblasts have a pivotal role to play in the immunopathology of VKC. CCL17 and CCL22 are chemokines that play an important role in Th2 cell-mediated inflammation in VKC, as it induces the recruitment of Th2 cells to the site of conjunctival allergic inflammation. These chemokines are produced by corneal fibroblasts activated by TNF-α and/or IL-4 during the allergic response [57].

In VKC, there are increased levels of eotaxin and IL-8, which correlate with increased infiltration of eosinophil and neutrophil in the conjunctiva [194]. Levels of activated eosinophils in tears, serum, and conjunctiva of patients with VKC is significantly higher compared to other allergic eye diseases [194, 195]. Additionally, CCL11/CCR3, CCL24/CCR3, and CCL26/CCR3 interactions are responsible for eosinophil infiltration in VKC. CCL11 (eotaxin-1), CCL24 (eotaxin-2), and CCL26 (eotaxin-3) expressed on ocular surface epithelial cells create a chemokine gradient that facilitates access of eosinophils to the conjunctiva and cornea in patients with VKC [196]. Conjunctival fibroblasts are known to prolong the survival of eosinophil that accumulate in the conjunctiva [57]. Eosinophil-derived granule proteins are epitheliotoxic to the corneal epithelium, and as such, they are responsible for breaching the corneal barrier function in VKC [174]. Eosinophil-derived granules such as eosinophil cationic protein (ECP) and eosinophil major basic protein (EMBP) disrupt the corneal epithelium while MMPs degrade the corneal basement membrane and stroma [185, 193]. The presence of ECP in the tears is an indication of increased levels of activated eosinophils [193]. MMP-2 and MMP-9 in tears of VKC patients mediates the degradation of collagen type IV and laminin in the corneal basement membrane. Activated eosinophils, epithelial cells, and fibroblasts are known to express MMP-2 and MMP-9, resulting in an increase in the level of MMPs at the ocular surface [57, 194]. Eosinophil-derived granule proteins and MMPs participate in the pathological mechanism of corneal damage by causing damage or disruption to the barrier function of the cornea, which allows them access to corneal stroma to activate fibroblast to release chemokines [185]. A balance between synthesis and degradation of ECM protein is an important aspect of the metabolism of ECM protein and proteoglycan that is necessary for maintaining the structure [57]. Increased synthesis of ECM proteins by activated fibroblasts under allergic inflammatory condition is associated with an imbalance between MMP and tissue inhibitor of metalloproteinase (TIMP) that results in increased collagen deposition and extracellular matrix hyperplasia, which causes proliferative changes that lead to the formation of limbal papillary hyperplasia and giant papillae [57, 194]. Histologically, the proliferative lesion is composed of eosinophils, mast cells, Th2 cells, fibronectin, neutrophils, goblet cells, plasma cells, and collagen type I and III [35, 57]. Giant papillae are characterized by squamous hyperplasia of the conjunctival epithelium and presence of dense fibrotic tissue [193]. ECM proteins participate in allergic inflammation by augmenting the expression of pro-inflammatory cytokines by both eosinophils and macrophages attached to them. Additionally, ECM is a reservoir for cytokine and chemokine, and as such, release of ECM proteins by corneal and conjunctival fibroblasts activated by IL-4 in the setting of allergic reaction contributes to the persistent activation of inflammatory cells during allergic

inflammation of the ocular surface [57]. As such, conjunctival tissue inflammation, corneal damage, and conjunctival tissue remodeling in VKC are associated with increased deposition of collagen type I, III, IV, and V in the conjunctiva [194]. Growth factors such as vascular endothelial growth factor (VEGF) are expressed by conjunctival epithelial cells and fibroblasts, mast cells, macrophages, and eosinophils [57, 59, 119, 197]. VEGF plays a crucial role in the immunopathology of VKC, as it induces angiogenesis and vasopermeability. The leakage of plasma from these leaky capillaries into the extravascular space leads to edema and significant modifications in the ECM of the conjunctiva [119, 198]. Th2 cell-mediated tissue remodeling is responsible for the development of giant papillae, hyperplasia of the epithelium, extensive deposition of ECM components in the conjunctiva, peripheral corneal fibrovascular proliferation, and other corneal changes [68, 119, 198]. Eosinophils, mast cells and Th2 cells accumulate in the conjunctiva, when all these cells are activated, they produce mediators that are associated with tissue damage [191].

Inflammatory reactions and clinical manifestations in VKC occur as a result of the action of histamine, arachidonic acid metabolites, as well as cytokines and chemokines released by mast cells, T cells, and eosinophils [176, 184]. Chronic inflammation in VKC is associated with tissue remodeling, conjunctival fibroproliferative lesions/papillary hypertrophy, limbal stem cell deficiency, squamous metaplasia of the ocular surface, and corneal epithelial defects [176, 199]. The clinical features of VKC include burning sensation, tearing, photophobia, blepharospasm, mucoid discharge, eyelid edema, conjunctival hyperemia and chemosis, perilimbal bulbar conjunctival hyperpigmentation, pseudogerontoxon, Horner-Tranta dots, shield ulcer, persistent corneal epithelial defects, and vernal plaques [68, 200–202]. In moderate to severe forms of VKC, hyperemia and papillary hypertrophy of the superior palpebral conjunctiva may partially obscure visualization of the deep tarsal conjunctival vessels [201, 203]. Perilimbal bulbar conjunctival or circumcorneal hyperpigmentation, seen as a fine golden brown pigmented perilimbal thickening, is due to excess pigment production by activated and proliferating melanocytes in the limbus [204]. Perilimbal bulbar conjunctival hyperpigmentation is associated with VKC, and it is an indication of limbal involvement in the immunopathology of VKC [205]. Limbal VKC is characterized by the presence of multiple gelatinous limbal infiltrates, Horner-Tranta dots, and pannus of the limbus (Fig. 4) [82]. Horner-Tranta dots found on the limbus are composed of clumps of necrotic eosinophils, epithelial cells, and neutrophils, and they usually disappear when the inflammatory reaction abates [8, 156, 206]. Conjunctival giant papillae on the superior palpebral conjunctiva and limbus are considered the hallmark features of VKC [178]. Corneal involvement is present in more than 50% of VKC patients; however, the cornea is an immunological privileged tissue that consist of epithelial cells, fibroblasts, endothelial cells, macrophages, and dendritic cells [59]. Activated corneal epithelial cells and fibroblasts participate in the immunopathology of VKC that leads to the development of corneal findings such as persistent corneal epithelial defects, epithelial macroerosion, shield corneal ulcer, corneal plaque, cornea ectasia, pseudogerontoxon, and corneal fibrosis [57, 59, 68, 119, 180, 207, 208]. Chronic inflammation of the ocular surface mediated by eosinophil-derived granule proteins and mediators released by inflammatory cells have an adverse effect on the limbal

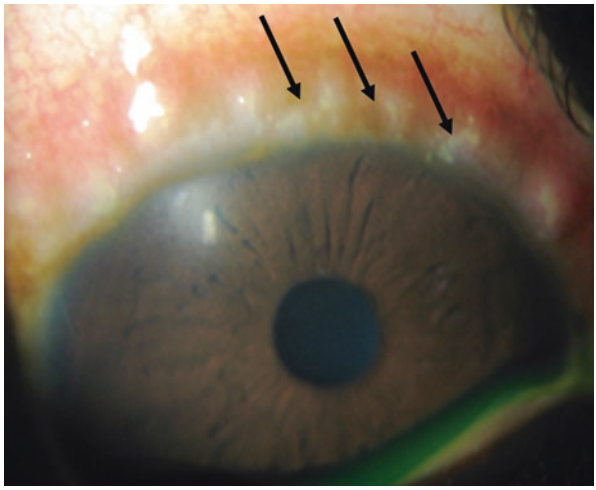

Fig. 4 Limbal VKC characterized by the presence of gelatinous limbal infiltrates with Horner-Tranta dots (black arrow)

epithelium and stroma causing direct damage to progenitor limbal stem cells, which results in the development of limbal stem cell dysfunction [8, 185, 199, 205]. Corneal or vernal shield ulcer in VKC is a vision-threatening oval shaped ulcer usually located in the superior third of the cornea [68, 76, 178, 180, 209]. Corneal shield ulcer has been reported to be more common in patients with the tarsal form of VKC [178]. The pathogenesis of vernal shield ulcer is believed to be due to: (1) chronic mechanical abrading of the corneal epithelium by giant papillae on the superior palpebral conjunctiva associated with the blink action, (2) breakdown of the barrier function of the corneal epithelium and degradation of corneal basement membrane, and (3) stroma caused by mediators produced by inflammatory cells and degranulated mast cells, and MMPs secreted by activated corneal fibroblasts and eosinophils [122, 180, 210–212]. Corneal plaque is formed when VKC-induced ulcer takes on a translucent appearance due to the deposition of inflammatory debris composed mainly of eosinophil-derived cytotoxic mediators at the base of the ulcer [180, 213, 214]. VKC is associated with corneal ectatic disorder such as keratoconus, pellucid marginal degeneration, and keratoglobus [194]. Corneal ectasia in VKC is due to thinning of the central cornea that results from apoptosis of keratocytes in the corneal stroma and/or degradation of corneal stroma due to the increase in matrix-degradative enzymatic activity [193]. Pseudogerontoxon, a gray-white lipid deposit in the peripheral cornea, is considered clinical evidence of previous allergic eye disease that results from prolonged infiltration of the limbus [68, 82, 215]. Shield ulcer, corneal plaque, corneal ectasia, and limbal stem cell deficiency are complications that involves the cornea in patients with VKC [185].

4.4.2 Diagnosis, Management, and Prognosis

The diagnosis of VKC is based on the presence of clinical signs and symptoms due to Th2 cell-mediated immunopathology. The main objective of clinical management in VKC is to suppress the allergic inflammatory process using non-pharmacological and

pharmacological treatment modalities. Avoidance of trigger factors and eye rubbing is important, since chronic eye rubbing can mechanically degranulate conjunctival mast cells leading to release of inflammatory mediators that play a role in the immunopathology of VKC [82, 195]. Although patients with VKC may benefit from supportive therapy and antihistamine/mast cell stabilizer combination, pulse topical steroidal therapy is usually necessary to control the inflammatory process. Prednisolone acetate 1.0% ophthalmic suspension is usually the drug of choice when loteprednol etabonate 0.5% is not therapeutically effective in controlling the allergic inflammation [132, 178]. The main objective of treating VKC-induced shield ulcer is to promote re-epithelialization by inhibiting the release of pro-inflammatory mediators, eliminating or minimizing damage to corneal epithelium by mechanical trauma from giant papillae during blinking, and promoting healthy corneal epithelium by removing inflammatory material [210]. Therapeutic bandage contact lens and/or prophylactic antibiotic ointment with anti-MMP activity are beneficial as adjunctive therapy in a VKC-related ulcer, since it reduces pain and promotes corneal re-epithelialization via protection of the fragile corneal epithelium during the corneal wound repair process [216]. Additionally, therapeutic bandage contact lens reduces the effect of blink action, which prevents giant papillae on the superior palpebral conjunctiva from inducing mechanical abrasion of the corneal epithelium [217]. There may be a role for amniotic membrane transplantation (AMT) in the management of VKC-associated shield ulceration, as it facilitates re-epithelialization by reinforcing adhesion of corneal epithelial cells as well as minimizing corneal scarring associated with proliferation of activated corneal fibroblasts. Additionally, AMT protects the corneal epithelium from mechanical trauma of giant papillae during blink action and prevents access of eosinophil-derived granule proteins to the cornea [210]. Majority of corneal vernal plaque requires anti-inflammatory therapy and surgical therapy to remove the plaque [180]. Disease-related complications of VKC that induce visual impairment are due to central corneal scar, shield ulcer, limbal stem cell deficiency, irregular cornea, and corneal ectasia (e.g. keratoconus). Treatment-related complications include steroid-induced cataracts and raised intraocular pressure [68, 177, 181, 210]. Long term prognosis is usually good with majority of patients with VKC having spontaneous resolution of the disease 4–10 years after onset [76].

5 Pharmacotherapy of Allergic Eye Disease: Current and Future

The management of allergic eye disease ranges from non-pharmacological to pharmacological modalities. The primary management of allergic eye disease is to remove or avoid the offending agent that triggers the allergic response in the eye. Management of allergic eye disease with pharmaceuticals becomes necessary when non-pharmacological approach fails to control the allergic immune response [117]. The following paragraphs will review most of the pharmaceutical agents used in the management of allergic eye disease (Table 2).

Table 2 Ophthalmic agents used in pharmacotherapy of allergic eye disease

Medication generic (brand)	Mechanism of action	Clinical uses	Daily Dosage
Alcaftadine 0.25% Rx (Lastacaft)	H1 receptor antagonist and mast cell stabilizer	Prevention of itching associated with AC	1 drop QD
Azelastine hydrochloride 0.05% Rx (Optivar)	H1 receptor antagonist and mast cell stabilizer	Treatment of itching associated with AC	1 drop BID
Bepotastine besilate 1.5% (Bepreve), Rx	H1 receptor antagonist and mast cell stabilizer	Treatment of itching associated with AC	1 drop BID
Epinastine hydrochloride 0.05% (Elestat), Rx	H1 receptor antagonist and mast cell stabilizer	Prevention of itching associated with AC	1 drop BID
Ketotifen fumarate 0.025% (Zaditor)	H1 receptor antagonist and mast cell stabilizer	Prevention of itching associated with AC	1 drop BID
Olopatadine hydrochloride 0.1% (Patanol), Rx	H1 receptor antagonist and mast cell stabilizer	Treatment of signs and symptoms of AC	1 drop BID
Olopatadine hydrochloride 0.2% (Pataday), Rx	H1 receptor antagonist and mast cell stabilizer	Treatment of ocular itch associated with allergic conjunctivitis	1 drop QD
Olopatadine hydrochloride 0.7% (Pazeo), Rx	H1 receptor antagonist and mast cell stabilizer	Treatment of ocular itch associated with allergic conjunctivitis	1 drop QD
Nedocromil sodium 2.0% (Alocril), Rx	Mast cell stabilizer	Treatment of itching associated with allergic conjunctivitis	1 drop BID
Ketorolac tromethamine 0.5% (Acular), Rx	COX inhibitor	Temporary relief of itching in AC	1 drop QID
Fluorometholone ophthalmic (FML 0.1%, FML Forte 0.25%), Rx	Inhibit edema, capillary dilation, leukocyte migration, and fibroblast formation associated with inflammation	Treatment of steroid-responsive inflammation of the conjunctiva, cornea, and anterior segment conditions	1 drop QID
Loteprednol etabonate ophthalmic 0.2% (Alrex), Rx	Inhibit edema, capillary dilation, leukocyte migration, and fibroblast formation associated with inflammation	Treatment of signs and symptoms of AC	1 drop QID
Loteprednol etabonate ophthalmic 0.5% (Lotemax), Rx	Inhibit edema, capillary dilation, leukocyte migration, and fibroblast formation associated with inflammation	Treatment of steroid-responsive inflammation of the conjunctiva, cornea, and anterior segment conditions	1 drop QID
Prednisolone acetate ophthalmic (Pred Forte 1%), Rx	Inhibit edema, capillary dilation, leukocyte migration, and fibroblast formation associated with inflammation	Treatment of steroid-responsive inflammation of the conjunctiva, cornea, and anterior segment conditions	1 drop QID

H1, Histamine 1; AC, allergic conjunctivitis; COX, cyclooxygenase; BID, twice daily; QD, once-daily; QID, four-times-a-day

5.1 Antihistamines

Antihistamine are used in the treatment of allergy including allergic eye disease. They are H1R antagonist with first generation antihistamines having sedative effect due to its lipophilic nature that allows these drugs to cross the blood brain barrier to block histamine-mediated central neurotransmission. Second generation antihistamine has an improved side effect profile with low sedative potential [117]. Cetirizine is a piperazine derivative that possesses histamine receptor inverse agonist effect with the added feature of inhibiting chemotaxis of eosinophils. Cetirizine has a low sedative potential and it is well tolerated in patients with allergic rhinoconjunctivitis [218, 219]. Loratadine is another long acting second-generation antihistamine with low sedative potential. It is safe and efficacious in treating allergic rhinoconjunctivitis, an effect that could be attributed to its inhibitory eosinophil activation [220–222]. Topical ophthalmic antihistamine has inverse agonist effect on H1 receptors. Because of the systemic effect of oral antihistamine and reduced systemic absorption of topical antihistamines, it is preferable to treat allergic eye disease with topical antihistamines [117]. Levocabastine hydrochloride 0.05% and emedastine difumarate 0.05% are ophthalmic antihistamines with potent selective histamine type 1 receptor inhibitory effect [68, 223, 224]. These topical antihistamines are dosed one drop four times daily for relieving the symptoms and signs of AC [225].

5.2 Mast Cell Stabilizers

Topical mast cell stabilizers are anti-allergic pharmaceutical agents that block the release of mediators of allergic eye disease from mast cells by blocking the degranulation of conjunctival mast cells [223, 226]. Mast cell stabilization is achieved via the blockade of calcium influx across the cell membrane. They have no effect on allergic expression due to already released histamine [75, 195]. Nedocromil sodium 2% ophthalmic solution, a pyranoquinolone dicarboxylic acid, is a mast cell stabilizer that is safe and effective for treating AC in patients age two and up. It stabilizes the mast cell by inhibiting the influx of calcium into the mast cell [117, 133, 223, 227, 228]. It could be considered a multiple anti-allergic agent due to its inhibitory effect on eosinophil [229]. Another action of nedocromil sodium includes reducing the ability of conjunctival epithelial cells to express ICAM-1 [229, 230].

5.3 Multimodal or Dual Acting Agents

Multimodal anti- allergic pharmaceutical agents possess inverse agonist effect on H1 receptors and mast cell stabilizing effects. These multimodal anti-allergic agents provide immediate symptomatic relief from histamine-induced effects and block the

release of pro-inflammatory and pro-allergic mediators by stabilizing conjunctival mast cells [231]. Olopatadine hydrochloride (0.1%, 0.2% and 0.7%) ophthalmic solution has selective inverse agonist effects on H1 receptors and prevent the release of pro-inflammatory and pro-allergic mediators from conjunctival mast cells, which translates into a prolonged clinical effect [223, 232, 233]. Olopatadine also reduce the recruitment of inflammatory cells into the conjunctiva by inhibiting the upregulation of ICAM-1 expression on conjunctival epithelial cells [229]. Olopatadine 0.1% formulation is dosed one drop twice a day whereas olopatadine 0.2% and 0.7% formulations are dosed one drop once daily. Olopatadine is indicated for the treatment of the signs and symptoms of AC [232, 234]. It is effective and well tolerated in patients age 3 and older [68, 200]. Azelastine hydrochloride 0.05% ophthalmic solution is a phthalazinone derivative that has a rapid onset of action and prolonged clinical effect. It has inverse agonist H1 receptor effect that attenuates histamine-induced allergic expression associated with early phase allergic response and exhibits mast cell stabilizing effect [229, 230]. Azelastine can reduce the accumulation of inflammatory cells at the site of allergic reaction in the conjunctiva by downregulating the expression of ICAM-1 by conjunctival epithelial cells. It is indicated for the treatment of ocular pruritus associated with AC. It has a noticeable unpleasant or bitter taste due to passage of the drug across the lacrimal duct via the nasal cavity [223, 235–237]. Ketotifen fumarate 0.025% is a benzocycloheptathiophene derivative that possesses a potent H1 receptor antagonist effect and mast cell stabilizing properties [223, 229, 238]. Additionally, it inhibits the accumulation of eosinophil at the site of allergen-induced inflammation in the conjunctiva [68, 117, 229, 230]. Ketotifen fumarate exhibits a biphasic effect on mast cell stabilization by inhibiting histamine release at low concentration and stimulating the release of histamine at higher concentrations [229, 230]. It is indicated for preventing ocular itch associated with AC [230]. It is available over-the-counter and it is dosed one drop twice daily. Epinastine hydrochloride 0.05% has affinity for H1 and H2 receptors and it has a prolonged therapeutic effect attributed to mast cell stabilization, inverse agonist effect on histamine receptors, and inhibition of the recruitment of neutrophil and eosinophil to the site of allergic reaction in the conjunctiva [239, 240]. It is a well-tolerated anti-allergic therapeutic agent that is dosed one drop twice a day for the prevention of ocular itch associated with AC [239, 241]. Alcaftadine 0.25% is a tricyclic piperidine aldehyde with a potent inverse agonist effect on histamine receptors and mast cell stabilizing effect on mast cells. It has a high affinity for H1 and H2 receptors and low affinity for H4 receptors [242, 243]. The inhibitory effect on recruitment of immune cells such as eosinophil and mast cells could be attributed to its affinity for H4 receptors expressed on mast cells and eosinophils [242, 244, 245]. It is a well-tolerated and efficacious antiallergic agent that is dosed one drop once daily for the prevention of itching associated with AC in patients over the age of 2 [242, 243]. Bepotastine besilate 1.5% ophthalmic solution is a piperidine derivative that is dosed one drop twice daily for preventing ocular itch associated with AC in patients aged 3 and over. It has inverse agonistic effect on H1 receptors and a stabilizing effect on mast cells in the conjunctiva [246]. Bepotastine besilate can prevent the accumulation of immune cells at the site of allergic inflammation in the conjunctiva by inhibiting expression of ICAM-1 by conjunctival epithelial cells [247].

5.4 Nonsteroidal Anti-inflammatory Drug (NSAID)

NSAIDs are beneficial as adjunctive therapy in allergic eye disease, as it relieves itch and conjunctival hyperemia associated with allergic eye disease. NSAIDs are considered steroid-sparing therapy, since they inhibit the production of prostaglandin E2 (PGE2) and PGI2 that lowers the threshold of the conjunctiva to histamine-associated ocular itch [117]. Ketorolac 0.5% is a topical NSAID that has been shown to diminish ocular pruritus and conjunctival injection associated with AC via the inhibition of cyclooxygenase (COX)-1 and COX-2 enzymes without having an effect on the size of the papillae on the conjunctiva tissue [68, 176]. In patients with triad of asthma, nasal polyps, and aspirin sensitivity, use of ocular NSAIDs could result in NSAID-induced asthma [117, 228].

5.5 Corticosteroids

Corticosteroids have immunosuppressive, anti-inflammatory, and anti-proliferative effects, which are attributed to the ability of the steroid to inhibit edema, cellular infiltration, capillary dilation and permeability, fibroblast proliferation, collagen deposition, leukocyte migration, and scar formation associated with inflammation. Furthermore, corticosteroids increase the synthesis of lipocortin that blocks the enzymatic activity of phospholipase A2 required for arachidonic acid metabolism and subsequent production of prostaglandins and leukotrienes that participate in the late phase of allergic response. Moreover, corticosteroids reduce the amount of unbound histamine on the ocular surface by increasing histaminase, an enzyme that degrades histamine [248]. Corticosteroids also block the enzymatic action of histidine decarboxylase, an enzyme required for the production of histamine in mast cells [124, 223, 249, 250]. Corticosteroids inhibit the expression of cytokine, chemokine, adhesion molecules, and inflammatory enzymes by deactivating the inflammatory genes that encode these inflammatory mediators [251]. Loteprednol etabonate ophthalmic suspension is a cortienic acid-based derivative [248]. It is a highly lipophilic ester-based corticosteroid compared to ketone-based corticosteroids such as prednisolone acetate [135]. Loteprednol etabonate is a site-specific steroid, in which the active drug resides at the site of inflammation long enough to deliver its therapeutic effect with minimal adverse effects [135, 250, 252]. The rapid transformation into an inactive metabolite by esterase in the eye is responsible for the low toxicity potential of loteprednol [248]. It is of note that loteprednol etabonate 0.2% is indicated for treating signs and symptoms of AC whereas loteprednol 0.5% is indicated for treating steroid-responsive inflammation of the conjunctiva and cornea [253, 254]. Patients with AC and giant papillary conjunctivitis are responsive to loteprednol [133]. Prednisolone acetate is a drug of choice for moderate and severe VKC, if loteprednol etabonate is ineffective in controlling ocular surface inflammation [176]. Prednisolone acetate ophthalmic suspension is a corti-

costeroid that is administered one drop four times a day for the treatment of corticosteroid-responsive inflammation of the cornea and conjunctiva [255]. It is of note that long term use of topical steroidal therapy is associated with ocular adverse effects such as steroid-induced glaucoma, cataract, delayed wound repair and increased susceptibility to ocular infection [176]. Fluorometholone (FML) is a 21-deoxy-9-fluoro-6-methylprednisolone that has up to 30 times more anti-inflammatory activity than hydrocortisone. It reduces the clinical expression of VKC [133, 226]. FML 0.1% is indicated for the treatment of inflammation of the cornea and conjunctiva [256]. Because of the potency in controlling inflammation of the conjunctiva via suppression of recruitment and activation of pro-allergic and pro-inflammatory mediators in the early and late phase of allergic response, corticosteroids are considered appropriate for treating patients that present with acute flare ups and chronic allergic eye diseases [65]. It is judicious to use loteprednol for treating allergic eye disease due to its low absorption and enhanced index of therapeutic response [117]. Raised intraocular pressure, cataract, and low resistance to infection are adverse effects associated with the use of topical corticosteroids. This could be attributed to transactivating activity of corticosteroids, and as such, topical corticosteroids with potent trans-repressive effect with little or no transactivation effect, may reduce the side effects associated with currently used topical corticosteroids [251]. Because of the chronic nature of allergic eye disease requiring glucocorticoid steroids with their associated adverse effects, there is a move towards developing steroids with little or no side effects. Selective glucocorticoid receptor agonists (SEGRA) are glucocorticoid corticosteroid-based therapeutic agents with trans-repression action and little or no transactivation effect. Mapracorat is a SEGRA that selectively reduces inflammation via inhibition of pro-inflammatory cytokines and activating anti-inflammatory proteins with reduced propensity to cause adverse ocular side effects that occur with glucocorticoids. Mapracorat has a decreased ability to activate gene transcription via binding to glucocorticoid response element but primarily transrepress genes. Thus, it has potent anti-inflammatory activity with low propensity to induce adverse reactions. Furthermore, mapracorat can inhibit release of proinflammatory cytokines and chemokines from corneal epithelial cells and fibroblasts [184].

5.6 Immunomodulators

Tacrolimus and Cyclosporine are immunomodulators that inhibit calcineurin, a phosphatase that activates transcription factors required for the production of IL-2 [160, 257]. Immunomodulators are also capable of inhibiting the proliferation of mast cells and reducing the recruitment of eosinophils [226]. Tacrolimus is a potent macrolide immunosuppressant that is therapeutically beneficial for patients with atopic dermatitis and patients with AKC [117, 160, 258–260]. Tacrolimus inhibits T cell activation by binding to immunophilin FK-binding protein (FKBP-12), which in turn, blocks calcineurin, an intracytoplasmic signaling protein downstream from

calcium-dependent calmodulin activation. Inhibition of calcineurin leads to inhibition of IL-2 transcription. Tacrolimus can inhibit the release of histamine and production of lipid mediators from basophils [261]. Tacrolimus has great potential of being a steroid-sparing agent for treating patients with chronic allergic eye diseases due to its enhanced safety profile and lack of adverse effect associated with steroid use such as skin atrophy, increased intraocular pressure, and reduction in collagen synthesis [262, 263]. Cyclosporine is a cyclic undecapeptide that mediates the inhibition of calcineurin, a phosphatase that is required for dephosphorylating nuclear factor of activated T cells (NFAT), which enables NFAT to translocate into the nucleus where it induces the transcription of cytokine genes [160, 257, 263]. Cyclosporine exerts its immunosuppressant effect by blocking the production of IL-2 and IFN-γ, thus reducing T cell-mediated inflammation [176, 201, 261]. Keklikci and associates [201] showed that administration of topical cyclosporine 0.05% for 12 weeks was efficacious in improving clinical features of VKC. Spadavecchia and colleagues [188] demonstrated the efficacy of using topical cyclosporine 1.0% in treating patients with severe VKC. Topical cyclosporine 0.05% (4–6 times daily) has been effective in treating patients with VKC and AKC [117, 257, 263].

5.7 Allergen Specific Immunotherapy

This immunotherapy is based on the principle of inducing immune tolerance via the exposure to allergen and it involves administration of allergen extracts in small increments to induce allergen-specific clinical tolerance to the inciting allergen [126, 263, 264]. To induce conjunctival immune tolerance using allergen-specific immunotherapy, eye drops containing specific-allergen to the conjunctiva are administered to the eye in gradual increments over a period of time with the intent of inducing increased tolerance to the allergen. The ultimate goal is to control clinical expression of allergic response without reliance on antiallergic pharmaceutical agents [265].

5.8 Pipeline/New Pharmaceutical Agents

A number of pharmaceutical agents are in various stages of trials that may likely be added to the current therapeutic agents for treating allergic eye disease. Ocular therapeutics Inc. have started enrolling patients for the second phase 3 clinical trial with the intent of evaluating the efficacy and safety of Dextenza (sustained release dexamethasone) 0.4mg intracanalicular depot for treatment of AC [266]. However, it has been announced that the phase 3 clinical trial was successful. Nicox have completed two phase 3 trials of ocular cetirizine, a topical ophthalmic histamine receptor blocker and mast cell stabilizer for the treatment of

ocular itching associated with AC [267]. The FDA recently approved ocular cetirizine (Zerviate) 0.24% ophthalmic solution dosed twice daily for ocular itch associated with allergic conjunctivitis. Future studies could focus on assessing the potential role of monoclonal antibody against adhesion molecule such as ICAM-1, as therapy for chronic allergic eye disease [194]. Immunomodulators, monoclonal antibody-based immunotherapy, allergen specific immunotherapy, and other new drugs in the pipeline are geared towards developing therapeutic modalities that are an improvement on the current anti-allergic agents or agents that target specific mediators of inflammation or immune cells that play a major role in the immunopathogenesis and immunopathology of allergic eye diseases. In managing patients with allergic eye disease, it is important to categorize or stage the severity of the ocular condition as well as educate the patient on the nature of the allergic eye disease and various pharmacotherapeutic strategies available to treating allergic eye disease. The use of one-a-day or twice a day dosed anti-allergic agents for prophylactic and therapeutic purposes are beneficial, since it does not impact on the lifestyle of the patient because such a drug regimen promotes compliance particularly in individuals with busy life styles such as students and workers. Majority of patients with allergic eye disease benefit from supportive therapy and steroid-sparing antiallergic medications. However, short term use of steroidal therapy would be necessary when allergic eye disease does not respond to conventional antiallergic therapy [132].

5.9 Potential Role of Probiotics

It is noteworthy that the lack of exposure to microbiota during the developmental stage of the immune system is likely to tilt the Th1/Th2 immune balance to favor Th2 immunity, since allergic disorders are associated with Th2 immunity along with activation of Th2-derived cytokines. Immune cells within the conjunctiva are affected by resident ocular microbiome, and the relationship between commensal microbiome and immune cells in the ocular surface is required to modulate ocular mucosal immunity [268]. It is of note that ocular surface microbiota plays a role in strengthening the ocular surface barrier function as a constituent of the ocular innate immunity, and depletion of ocular commensal microbiome via use of topical antibiotics is likely to have an impact on the ocular surface barrier function [269]. As such, use of probiotics to induce a Th1 immune response during the early development of the immune system has the potential to shift the Th1/Th2 immune balance towards Th1 immune response [270]. There are reports in the scientific literature of reduction of ocular and nasal symptoms in patients with perennial allergic rhinoconjunctivitis following intake of yogurt supplement containing Bifidobacterium longum and fermented milk containing Lactobacillus paracasei-33. Potential benefits of probiotic as an adjunctive therapy for patients with allergic rhinoconjunctivitis needs further studies to confirm its benefits [271, 272].

6 Conclusion and Future Perspectives

Allergic eye disease is mediated mainly by IgE and/or Th2 cells along with pro-allergic and pro-inflammatory mediators participating in the immunopathogenesis and immunopathological process. Cytokines, chemokines, histamine, adhesion molecules, MMPs, and lipid mediators are important mediators that participate in allergic immune responses. Epithelial cells and fibroblasts are non-immune cells that play a role in the immunopathology of allergic eye disease when they become activated by pro-allergic and pro-inflammatory mediators. Th2 cells, mast cells, and eosinophils are the major immune cells that participate in the immunopathogenesis and immunopathology of allergic eye diseases. The major forms of allergic eye diseases that have an impact on conjunctiva and/or cornea include AC, GPC, AKC, and VKC have been discussed. AC is predominantly an IgE-mediated ocular surface disease, in which, activated mast cells undergo degranulation leading to the release of histamine and other mediators that cause the clinical features of AC [2, 123]. GPC is a multifactorial inflammatory state of the conjunctiva with immune and non-immune aspects involved in the pathogenesis. Th2 cells, mast cells, IgE, neutrophils, monocytes, and complement mediators of inflammation play a crucial role in the immunopathogenesis and immunopathology of the ocular condition [141]. AKC is a severe allergic eye disease, in which, chronic mast cell degranulation and T cell-mediated inflammation are involved in the immunopathology of the ocular condition with consequential tissue damage and remodeling of the conjunctiva and cornea [167]. VKC is a recurrent ocular surface inflammation mediated predominantly by Th2 cells with major effector cells and mediators participating in the development of fibroproliferative lesions as well as damage and remodeling of the cornea and conjunctiva [68].

Since mast cells are major effector immune cells in allergic eye diseases, histamine, lipid mediators, and cytokines released by degranulated mast cells are targets for current anti-allergic therapeutic agents. However, research and development geared towards more potent mast cell stabilizers should be considered an important future direction to focus on preventing release of mediators. Th2 cells generate cytokines that are involved in generating plasma cells that produce IgE that bind to FcεRI on conjunctival mast cells as well as cytokines that activate important immune effectors of allergic eye disease such as mast cells and eosinophils. IL-1, IL-4, and IL-5 are major cytokines that play a crucial role in immune responses in allergic eye disease. IL-4 is involved in mediating B cell proliferation and differentiation as well as in inducing fibroproliferative lesions in the conjunctiva. IL-5 is involved in activating eosinophils that have a toxic effect on the epithelial cells of the ocular surface with associated tissue damage and remodeling. IL-1 is also involved in the inflammatory process of the ocular surface via interaction with IL-1R on epithelial cells of the ocular surface. Immunotherapy that targets these cytokines and their receptors with the intent of attenuating the induced immunopathogenesis and immunopathology would be beneficial for these patients with allergic eye disease. Adhesion molecules such as ICAM-1 are involved in the immunopathology of allergic eye disease,

and they are upregulated during the inflammatory process with the intent of recruiting immune cells to the site of allergic inflammation [39]. Histamine and their receptors participate in the immunopathology of allergic eye disease. Histamine has effects on tissue and cells of the ocular surface with associated tissue changes. Activation of histamine receptor type 1, 2 and 4 are associated with various allergic expression involving the ocular surface, and histamine/H4R mediates recruitment of eosinophil and Th2 cells that exacerbate the allergic inflammation in the ocular surface with consequential tissue damage and remodeling [8, 70]. Chemokines are important for recruiting immune cells to the site of allergic inflammation, and blockade of chemokine and/or their receptors could attenuate inflammation in allergic eye diseases. Dendritic cells are important initiators of allergic eye disease, and they interact with $CD4^{+}$T cells to generate allergen-specific Th2 cells. Additionally, TSLP interacts with dendritic cells to promote the generation of allergen-specific Th2 cells [11]. As such, blockade of TSLP could be beneficial in preventing the allergic immune response from developing. A considerable understanding of cells and mediators in allergic eye disease and their respective roles in the immunopathogenesis and immunopathology of allergic eye diseases are crucial to providing significant insight on how to manage the diseases with the intent of controlling inflammation and preventing tissue damage and remodeling as well as developing pharmacotherapy and immunotherapy that would be beneficial as prophylactic and/or therapeutic agents.

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