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Review Article

Development in therapeutic strategies for allergic conjunctivitis

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ABSTRACT

Conjunctivitis, also known as pink eye, is a conjunctival inflammation. It is brought on by bacteria, viruses, toxins, and allergies, including coronaviruses, the most frequent reason being allergic conjunctivitis (AC), which is brought on by exposure to pollutants like pollen, animal hair, or mold. The primary contributor to it is the linkage of immunoglobulin E caused by allergens and receptors on stimulated conjunctival mast cells. As a consequence, mast cells are degranulated, along with the release of histamine, cytokines, chemokines, and lipid mediators. The particular eye tissues impacted and the immune mechanism(s) (both local and systemic) that are involved all play a role in the clinical course, length, intensity, and co-morbidities. It frequently occurs in conjunction with allergic rhinitis, also known as allergic rhino-conjunctivitis and other allergy conditions. Atopic keratoconjunctivitis, giant papillary conjunctivitis, seasonal and perennial conjunctivitis, and vernal keratoconjunctivitis are the different types of allergic conjunctivitis. Ocular allergies are frequently misdiagnosed and undertreated, despite the emergence of innovative therapeutic strategies. This review focuses on several previously published studies to discuss the available therapeutic options for treating allergic conjunctivitis as well as the potential targets for the therapies. The association of conjunctivitis with COVID-19, along with recent patents and research, has also been explored.

Keywords: Allergic Conjunctivitis; Seasonal and Perennial Allergic Conjunctivitis; Vernal Keratoconjunctivitis; Atopic Keratoconjunctivitis; Giant Papillary Conjunctivitis; Treatments; Potential Targets

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1. Introduction

The conjunctiva is a transparent, vascularized mucosal membrane that surrounds the front of the sclera and the inside of the eyes. The bulbar, lateral, superior, and inferior conjunctival fornices, as well as the palpebral conjunctiva, are its sections. It lines the scleral surface of the globe and the inner surface of the eyelids (the palpebral conjunctiva). It is made up of epithelium and subepithelial stroma (the bulbar conjunctiva). It has a substantia propria and a surface epithelium. The conjunctiva's major known functions include supplying the tear film with mucus and shielding the ocular surface from pathogens by acting as a physical barrier as well as a source of inflammatory cells[1]. Since the conjunctiva is continuously exposed to the environment and nearby allergens, it has an active immune system. The palpebral and bulbar conjunctiva is shown in **Figure 1**.

The term "conjunctivitis" signifies infection or inflammation in the conjunctiva. It may be chronic or acute, or non-infectious or infectious. In contrast to chronic conjunctivitis, which is defined as lasting longer than a month, symptom lasts 3 to 4 weeks from the presentation and in the case of acute conjunctivitis (typically

only lasting 1 to 2 weeks)[2]. Because there is no single cause for this increase, experts are looking at a variety of potential causes, such as genetics, urban air pollution, pets, and early childhood exposure. There are numerous causes for infectious conjunctivitis, including bacterial, viral, chlamydial, fungal, and parasitic conditions. Adenoviruses cause most cases of viral conjunctivitis. Bacterial conjunctivitis is mostly caused in children. In adults, the most common causes are *Haemophilus influenza, Streptococcus pneumonia*, and *Staphylococcus aureus*. In addition, *N. gonorrhea* is the most common source of infectious conjunctivitis in newborns. Common causes of conjunctivitis are shown in **Table 1**[3].

The most frequent cause of conjunctivitis is an allergic reaction, and it is more prevalent in the spring and summer seasons[4]. Allergic conjunctivitis occurs when allergens engage with IgE affixed to hypersensitive mast cells to cause an inflammatory reaction. The condition manifests clinically as an ocular allergy. Depending on the source of the sickness and the intensity of the clinical reaction, the illness can also be categorized as acute, hyperacute, or persistent[5]. The three most prevalent types of conjunctivitis based on traditional findings are listed in **Table 2**[2,6].

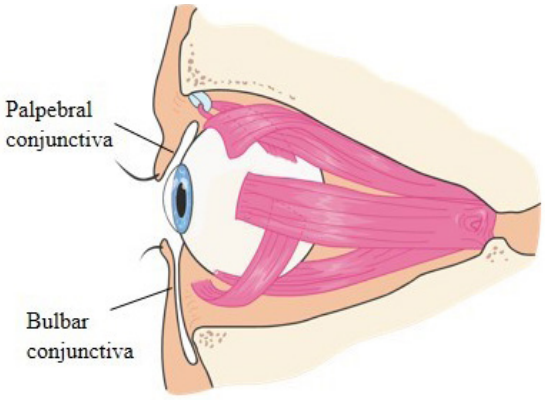

Figure 1. Conjunctiva of eye.

2. Diagnosis of conjunctivitis

Making the right choices regarding the care and management of the eyes requires a focused ocular examination and medical history[5]. Diffuse conjunctival redness that covers the whole area of the conjunctiva, including the tarsal and bulbar conjunctiva, should be the significant determinant of conjunctivitis. As the more serious conditions like keratitis, iritis, angle closure glaucoma, and keratitis

Table 1. Common causes of conjunctivitis

Infectious causes		
Viral pathogens	**Bacterial pathogens**	**Non-infectious causes**
Herpes zoster	*Haemophilus influenza*	Allergens
Enterovirus	*Streptococcus pneumoniae*	Toxin
Herpes simplex	*Staphylococcus aureus*	Irritants
Adenovirus	*Chlamydia diphtheria*	
Pox virus	*Corynebacterium diphtheria*	

Table 2. Types, symptoms, and choice of treatments

Types	**Symptoms**	**Choice of treatments**
Viral	Watery discharge History of recent upper respiratory tract infection Itching & tearing Tender preauricular lymphadenopathy Inferior palpebral conjunctival follicles Sore throat infection and fever	Antibiotics Antivirals NSAIDs Corticosteroids Povidone-iodine
Bacterial	Conjunctival papillae White, yellow, or purulent or mucopurulent secretion from the eyes in the morning Foreign body sensation and redness Conjunctival papillae Irregular lymphadenopathy	Antibiotics
Allergic	Burning or itching Frequent occurrence of atopy/allergies Watery secretion Edematous eyelids Conjunctival papillae No preauricular lymphadenopathy	Antihistamines NSAIDs Corticosteroids Mast cell stabilizers

do not affect the tarsal conjunctiva. If the redness is localized, think about a different diagnosis of a foreign body, episcleritis, or pterygium. Many common conjunctivitis symptoms, such as redness and discharge, are widespread, which makes determining the concealed cause more complicated[7]. Even though symptoms frequently coexist, a methodical way and a thorough physical and history test can securely rule out any severe diagnoses that could endanger your vision and direct you toward the conjunctivitis cause. The clinical presentation, however, is frequently nonspecific.

The following factors may be used as the basis for an overall diagnosis of conjunctivitis:

- Clinical evaluation and history
- Gram and Giemsa strain of conjunctival scraping
- Conjunctival scraping culture and recognition
- Conjunctival biopsy
- Immunoassay
- Polymerase chain reaction or
- Other diagnostic tests

Inspection of periocular and ocular tissues is part of the physical examination of patients who may have ocular allergies. To diagnose conjunctivitis, identify the underlying cause, and ultimately determine the best course of treatment, a thorough history must be studied. Visual acuity, corneal opacity, type of discharge, abnormal pupil shape or size, eyelid swelling, orbit protrusion, and throughout the physical eye examination, any asymmetry should be checked[8]. The presence of accompanying symptoms, such as an infection of the upper respiratory system or contact with people who have previously displayed these symptoms, points to a viral type of conjunctivitis. The different types of conjunctivitis may be distinguished using clinical examinations for dry eye (Schirmer test), unstable tear film, and lagophthalmos. Because of mucoid discharge and tearing, fluctuating blurring is typical. Photophobia is frequently mild. However, if any of these signs or symptoms are severe, it's crucial to rule out other conditions like meningitis, glaucoma, uveitis, keratitis, or carotid-cavernous fistula[9].

3. Allergic conjunctival diseases

The majority of immune-mediated diseases are caused by allergic conjunctivitis (AC). Perennial allergic conjunctivitis (PAC), seasonal allergic conjunctivitis (SAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC) are all allergic conjunctival disease classification. Despite certain shared allergy indicators, VKC and AKC have clinical and pathophysiological characteristics that are significantly different from PAC and SAC. Moreover, giant papillary conjunctivitis (GPC) associated with ocular prostheses or contact lenses is frequently categorized as an ocular allergy. Classification of allergic conjunctival diseases is depicted in **Figure 2** and classification based on the mediators is shown in **Figure 3**[10].

3.1 Seasonal and perennial allergic conjunctivitis

Several substances unique to each person can cause allergic conjunctivitis, which frequently affects people with allergic conditions. The two most frequent types of eye allergies are perennial allergic conjunctivitis (PAC) and seasonal allergic conjunctivitis (SAC). The intermittent terms (4 weeks) have

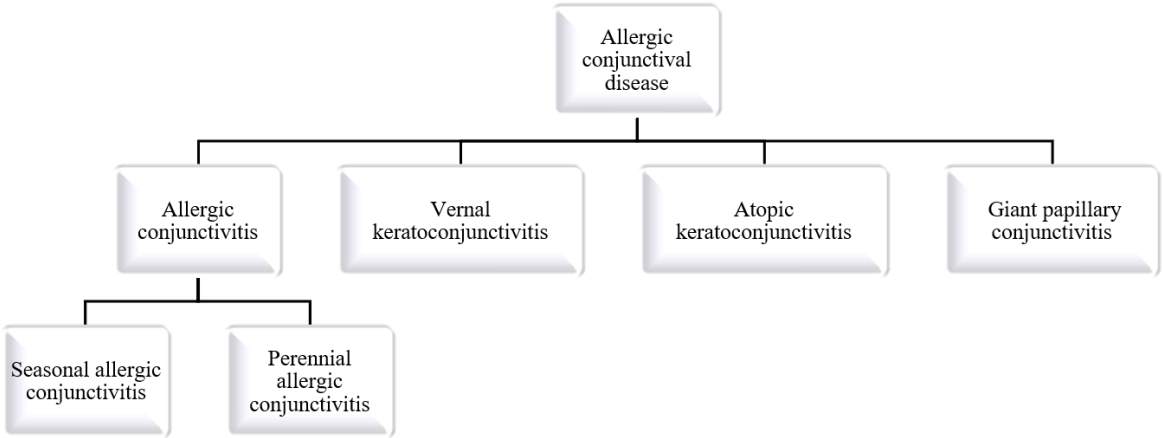

Figure 2. Classification of allergic conjunctival diseases.

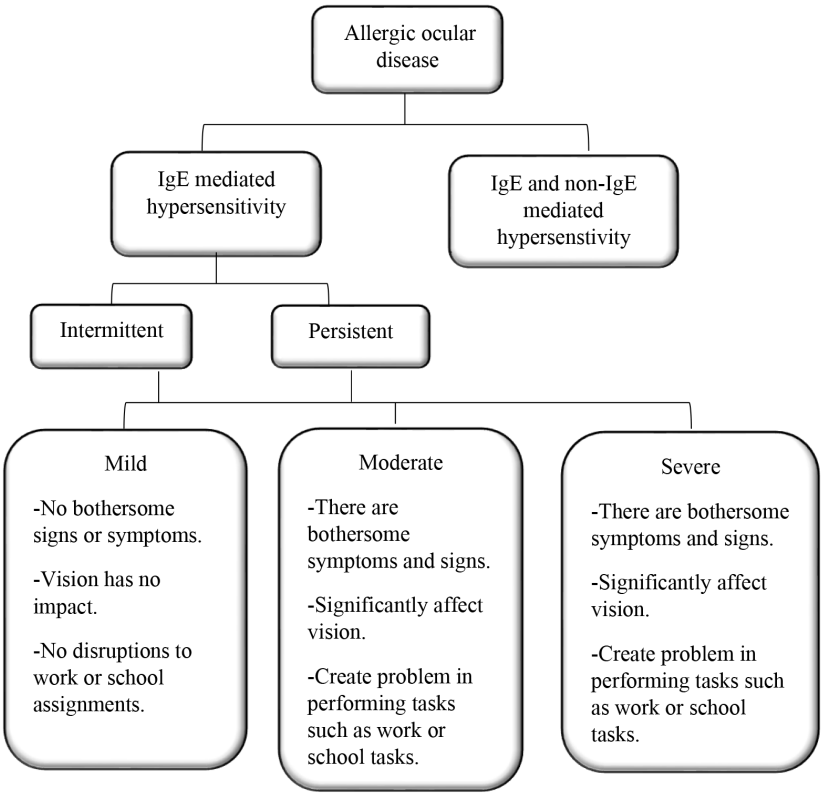

Figure 3. Classification based on the mediators.

been proposed by international consensus panels because the perennial and seasonal ones do not specify a duration[11]. Interaction of allergen with IgE that is bound to sensitized mast cells causes allergic conjunctivitis, which then presents clinically as an ocular allergy. IgE-mediated hypersensitivity reactions predominate in the pathogenesis of allergic conjunctivitis. Histamine, tryptase, prostaglandins, and leukotriene levels in tears are activated. Clinically, this quick or early response lasts for 20 to 30 minutes. Rhinitis, conjunctivitis, and allergic asthma all result from IgE-mediated allergies to environmental pathogens, so their etiology is identical[12]. The two conditions share the same signs and symptoms. The patient's specific allergens to which they are allergic make a difference. Pollens in the air are frequently to blame for SAC. Typically, symptoms and signs appear during the summer and spring and lessen during the winter season. With exposure to yearly allergens, PAC can happen all year long. Conjunctiva's redness, swelling, and itching are diagnostic indicators of SAC and PAC. It is uncommon to have corneal involvement[3]. It is acknowledged that AR-related ocular symptoms are often underdiagnosed and undertreated. Studies on SAC patients have shown that ocular symptoms, such as itching, burning, tearing, and conjunctival swelling and redness, have a detrimental effect on one's lifestyle quality. Few incidences of benign conjunctivitis typically occur in the majority of patients with ocular allergies. The patient's examinations must include a thorough ocular inspection, biomicroscopy, a Slit-lamp biomicroscopic examination, and additional supplemental diagnostic procedures like an aeroallergen skin probe test[13–15]. Even though there are several different types of ocular allergies, perennial and seasonal AC is the mildest and the most prevalent one. Vernal and atopic keratoconjunctivitis result in epithelium remodeling and, in rare instances, vision loss. Although it has been discovered that giant papillary conjunctivitis (GPC), more correctly known as contact lens papillary conjunctivitis (CLPC), is caused by repetitive microtrauma to nonimmune tissue, it is typically found in people who wear contact lenses.

3.2 Vernal keratoconjunctivitis

Vernal keratoconjunctivitis (VKC), is a chronic, severe, bilateral inflammatory eye condition that strongly influences children. The most common symptoms and indicators include itching, burning, tearing, and photophobia. Vernal (spring) implies that the disease has a seasonal preference, but its course typically lasts all year long, especially in the

tropics. And over 60% of patients experience additional occurrences in the wintertime, and since the disease's onset, 23% of patients have a persistent type of VKC. Furthermore, after a median of 3 years from the time of disease start, the seasonal (vernal) form transforms into a perennial, chronic inflammation in nearly 16% of cases, suggesting that the longer patients have VKC, the more likely they will develop an enduring form of the condition[16–18]. Eosinophils, Th2 cell mast cells, chemokines, adhesion molecules, and cytokines are all associated with the immunopathology and immunopathogenesis of VKC. Typically, conventional allergy conjunctivitis treatment is insufficient for VKC[17]. Around 50% of individuals with palpebral VKC have some degree of corneal engagement, which might include macro erosions, scarring, punctate epithelial erosions, infectious keratitis, and neovascularization[19]. The corneal involvement is there, even though it lacks mast cells, and lymphocytes, and has few immature resident dendritic cells. This inflammation manifests as ulcers, epithelial macro erosion, or superficial punctate keratitis[20]. Elevated levels of CD4+ Th2 cells and cytokine and co-stimulatory molecule expression in the conjunctiva indicate that T cells are majorly responsible for the growth of VKC. Pro-inflammatory cytokines, Th1-type cytokines, growth factors, a range of chemokines, and enzymes are all increased in patients suffering from VKC[21]. It is distinguished by thick mucus hypersecretion containing sticky mucous filaments, known as "ropy discharge". Eosinophils and epithelial cell debris are what are known as Horner-Trantas' dots, which are deposits or conjunctival yellow-white points or deposits of transient limbal[22]. The involvement of the cornea results in photophobia, pain, and a feeling of a foreign body. The changes to the cornea include shield sores, epithelium macro-erosions, late corneal vascularization, plaque formation, and punctate epithelial keratitis[23]. Although there are numerous options and each patient should receive a customized plan of care, there is currently no established gold-standard treatment algorithm for VKC. Any prescribed treatment plan should be started right away, and the patient should be closely watched for the emergence of any corneal complications. Topical treatment is the primary form of pharmaceutical therapy for VKC. The cornerstone of prophylaxis is mast cell stabilizers. Antihistamines may be helpful in less severe cases, but corticosteroid therapy may be necessary in more severe cases. Other immunomodulatory therapies have been thoroughly researched because the long-term use of steroids is linked to numerous complications[24].

3.3 Atopic keratoconjunctivitis

Atopic keratoconjunctivitis (AKC) is one of the most incapacitating allergic conjunctival diseases because it can lead to corneal complications that impair vision. The usual onset of AKC is in late puberty or early adulthood, although instances have been reported as early as the age of 7 years. It can last into the fourth and fifth decades of life, with a high occurrence between the ages of 30 and 50 years. Clinical symptoms of AKC include retinal detachment, giant papilla development, and keratoconus. Despite being categorized as an allergic conjunctival disease, AKC differs from the other subtypes in terms of clinical and pathophysiological characteristics. PAC and SAC are mainly founded on IgE-mast cell hypersensitivity with widespread mast cell activation, whereas VKC and AKC are a combination of IgE-mast cells and Th2-type allergy inflammation. The presence of activated eosinophils, T lymphocytes, and destructive enzymes associated with them, which are prominent in sight-threatening AKC and absent in non-sight-threatening allergic conjunctivitis, is the main difference between the two. Mast cells have increased significantly in SAC and PAC due to the mucosal type mast cell infiltration, but lymphocytes and eosinophils are insignificantly present. To manage allergic eye symptoms, systemic and topical antihistamine's gradual application can be implemented. Ocular erythema can be quickly relieved with topical vasoconstrictor medications, but the relief is only temporary, and using them excessively can cause rebound hyperemias and irritation. The immunomodulatory treatment used early in the disease's progression may prevent it from advancing to more serious versions. Betamethasone, dexamethasone, fluorometholone, and hydrocortisone are steroid eye drops that turned out to be successful in treating AKC; on the other hand, they may also raise intraocular pressure. Atrophy of the derma and herpes simplex keratitis are additional side effects that restrict the use of steroids. An immunophilin called cyclosporine A (CsA) prevents the release of

inflammatory mediators by inhibiting the activation of T lymphocytes, eosinophils, and mast cells as well as IL-2 receptor expression. Another calcineurin inhibitor, tacrolimus, reduces the expression of IgE receptor I on Langerhans cells and prevents the release of inflammatory cytokines such as IL2, IL3, IL4, IL5, IL8, TNF, and IFN. Tacrolimus as well as CsA both share some characteristics, but tacrolimus is thought to be 10–100 times more potent. When pharmacological treatment is ineffective and conjunctival papillary hyperplasia exacerbates corneal ulcers, surgery such as tarsal conjunctival resection may be an option[25–29].

3.4 Giant papillary conjunctivitis

Giant papillary conjunctivitis (GPC) is a form of inflamed eye illness distinguished by the appearance of "giant" papillae on the superior tarsal conjunctiva. According to recent literature, papillae having a diameter of 0.3 mm or greater are considered to be indicative of GPC. It is also known as allergic conjunctivitis and is caused by continuous interaction between the conjunctiva of the upper eyelid and a foreign substance, such as an ocular prosthetic, an open scar, or more frequently, contact lenses. It is not caused by a hypersensitivity mechanism. Giant papillary conjunctivitis (GPC) is also termed contact lens-induced papillary conjunctivitis (CLPC) when it has been brought on by wearing contact lenses. The type of contact lenses utilized has an impact on GPC prevalence as well. Although initially the application of hydrophilic contact lenses was found to be associated with this condition, it has now been linked to a wide range of contact lens materials. Compared to rigid lenses, soft contacts are more susceptible to causing GPC. The etiology is multifactorial and includes immune responses that result in both immediate and delayed hypersensitivities as well as mechanical trauma to the conjunctiva. In histopathology studies of people suffering from GPC, it has been found that the condition of the tarsal conjunctiva is more critical. When wearing contact lenses is temporarily discontinued, GPC is frequently treated with anti-allergy therapies. Dual-action medications, antihistaminic medications, and mast cell stabilizers are used in therapy. It has been demonstrated that a mast cell stabilizer (topical cromolyn sodium), works well for GPC when combined with good lens hygiene. Steroid eye drops are a suitable therapeutic choice when anti-allergic medication does not properly alleviate symptoms or extreme symptoms of GPC. Intraocular pressure(IOP) is one of the side effects of using steroids, and to reduce such side effects, "soft steroids" can be used. In a study removal of large papillae has been considered the best option for obstinate cases of GPC. Cryotherapy is also a better approach for the treatment and is also less invasive[30–34].

4. Relationship between allergic conjunctivitis and allergic rhinitis

Allergic conjunctivitis and allergic rhinitis share a close epidemiological relationship. Additionally, both ailments display comparable pathophysiologic mechanisms[35]. Allergic rhinitis is an allergic reaction due to tiny particles called allergens and is distinguished by rhinorrhea, nasal congestion, nasal itching, and sneezing. Allergic rhinitis, like allergy conjunctivitis, is an IgE-mediated illness[36]. The existence of a nasal-ocular reflex, which explains the connection between the pathologies of the nose and eyes, has been demonstrated in numerous investigations. The histamine-induced irritability of the nasal epithelium triggers a reaction, which is mediated by the autonomic nervous system. The symptoms are caused by this response, which is felt at the conjunctival level and the nasal cavity level[37]. Medication using antihistamines, topical decongestants, allergic-specific immunotherapy and patient education are the three main pillars for the treatment of allergic rhinoconjunctivitis.

Similarities in the inflammatory responses of the conjunctiva and the nasal mucosa include:

- Histamine-mediated inflammation.
- Inflammatory cells are recruited during the late-phase reaction.

Differences between the nasal mucosa's and conjunctivas' inflammatory responses are mentioned below:

- Higher nasal mucosa exposure to allergens as a result of nasal air vortices as opposed to air impaction on the conjunctival surface.
- Absence of late-phase eosinophil infiltration to the conjunctiva.

5. Conjunctivitis association with COVID

The worldwide coronavirus pandemic has shown broad and enduring effects on conjunctivitis. There is still much to learn about the disease's broad spectrum. The various presentations, the ongoing effects on various organs, and the pathogenesis theories[38]. Both animals and humans are susceptible to coronavirus eye infections. Animals can develop anterior uveitis, acute conjunctivitis, optic neuritis, and retinitis as ocular symptoms. According to the literature, the only ocular manifestation of conjunctivitis that has been recorded so far is acute conjunctivitis. Ophthalmologists have contracted COVID-19 and, unfortunately, some have even passed away. A report that one of them may have contracted the disease through the ocular mucosa and later displayed systemic symptoms sparked fear, raising the possibility that COVID-19 may first present as conjunctivitis and may then spread through infected patients' ocular secretions[39]. And also during the 2003–2004 coronavirus outbreak, conjunctival involvement, including watering and congestion, was observed but not later investigated. Additionally, accounts of conjunctival swelling in a small number of patients who tested positive for COVID began to surface as the COVID epidemic got underway. Although none of these hypotheses have been demonstrated, they include direct virus inoculation of the ocular mucous membrane, spread through the nasopharynx and lacrimal duct, and the lacrimal gland, and systemic spread taking place to the ocular surface[40,41]. The COVID-19 ocular surface signs may be delayed (after a week) or acute (within a week). Although diffuse follicular conjunctivitis may occur in any form, the immunological response is believed to have a significant role in the prolonged symptoms' onset. A standard pre-prepared package containing an antibiotic and lubricant can be given to the patient right away, for example,

- 3–6 times daily for 14 days of moxifloxacin hydrochloride 0.5% or ciprofloxacin hydrochloride 0.3%, and
- 3–6 times daily for 14 days, carboxymethyl cellulose 0.5% or sodium hyaluronate 0.1%.

Ibuprofen and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided and instead, oral acetaminophen can be used because they have been shown to exacerbate the systemic signs of COVID infection[42]. Topical steroids should be avoided as much as possible during the pandemic because we might not be able to regularly follow up with patients to check intraocular pressure. According to several ophthalmologists, there is currently a great deal of confusion regarding how to handle these conjunctivitis cases because people are nervous and afraid of new things. "Of course, you learn from certain moments, and you always get more and more experience, so maybe in the future you will do some different things, but in general, the basics always stay the same."—Max Verstappen.

According to numerous studies conducted in various nations, a sizable proportion of COVID patients can exhibit conjunctivitis symptoms, which are typically present at an early stage of the illness. One such study has been carried out in a hospital in Spain, where 35 patients were identified as having acute conjunctivitis out of the total 301 COVID patients. 301 individuals received ophthalmological examinations, and in addition to conjunctivitis, other eye diseases were discovered. In specific, all three patients with subconjunctival hemorrhages, four patients with mild pterygia, and two patients with hordeolum received cautious care. With the very inconsistent statistics being reported, conjunctivitis has not been fully quantified in COVID patients in terms of incidence and recurrence. Since the number of subjects with COVID-19 who exhibit conjunctivitis symptoms varies between studies. Another study conducted at Aravind Eye Center in Madurai, India showed the association between conjunctivitis and covid in almost 11% of the patients. Along with conjunctival scarring covid can also cause optic neuritis, uveitis, and keratitis[43–46].

6. Treatment approaches

It is optimal to target the underlying cause of conjunctivitis in treatment. Early detection and care can help preserve one's sight and, in some circumstances, even save one's life[47]. The main behavioral change for treating all types of allergic conjunctivitis is to avoid the offending antigen; however, because of the size of the eye's surface area, it is frequently impossible to protect the eyes from allergens present in the air. Artificial tear replacements serve as an obstacle and enhance conjunctival mu-

cosa's first line of defense. Steroid formulations, antihistamines, and mast cell-stabilizing drugs have been the basis of the therapy. Numerous allergies and inflammation factors that could be present on the eye surface are diluted and removed by these substances[48]. Pharmacologic treatments may be applied topically or administered systemically to lessen the allergic response when avoiding allergens and non-pharmacologic remedies are inadequate to properly relieve symptoms. The cornerstone of the treatment of eye allergy is the use of anti-allergic therapeutics such as multiple-action anti-allergic drugs, antihistamines, and mast cell inhibitors[3]. Interestingly, the vasoconstrictor naphazoline has been the first topical drug to be authorized by the American FDA for the therapy of eye hypersensitivity in 1971[10].

6.1 Topical antihistamines

Topical antihistamines (AH) temporarily reduce itching and redness by competitively and reversibly blocking histamine receptors as shown in **Figure 4**. They do not affect histamine production and release. Other pro-inflammatory mediators, like prostaglandins and leukotrienes, are unaffected by these medications and continue to function normally. It can be used topically or systemically, but for only a shorter duration of time[49]. Decongestant and antihistamine combination therapies are more successful. Examples of topical first-generation eye antihistamines include pheniramine and anthazoline; however, their use has been phased out in favor of more recent antihistamines that are better suitable for long-term use, such as 0.05% emedastine and 0.05% levocabastine[50]. Over first-generation antihistamines, second-generation antihistamines are better as they show lesser sedation. Since they have undergone substantial research over the past 30 years, newer generation AHs are safer, have an equivalent or quicker onset of action, and are more effective than older Ahs[51].

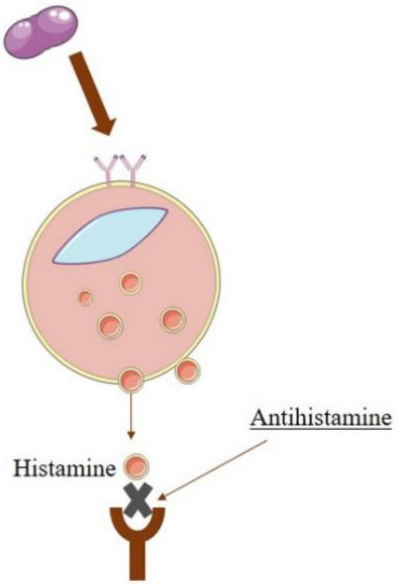

Figure 4. Mechanism of action of antihistamines.

6.2 Corticosteroids

It has been shown that the usage of corticosteroids can reduce the symptoms and signs and stop them from getting worse[52]. In addition to being effective in treating both types (chronic and acute) of AC, corticosteroids continue to be one of the most efficient pharmacologic treatments for the more extreme forms of ocular allergy. They have anti-proliferative and inhibitory properties because of their ability to block the transcription factor that affects the production of genes for Th2-derived cytokines, the development of stimulated T cells into Th2-lymphocytes and they also reduce the number of eosinophils and mast cells and obstructs the chemotaxis of inflammatory cells in conjunctiva as shown in **Figure 5**. A promising therapy for acute conjunctivitis may involve corticosteroids combined with antibiotics[53]. Corticosteroids have some drawbacks, such as ocular side-effects like cataract formation, slow wound healing, increased intraocular pressure, and secondary infections. These medications are thus effective for brief courses (up to 14 days), but if longer courses are required, an eye examination should be conducted along with measurement of intraocular pressure and a baseline evaluation of cataracts. To avoid the serious eye adverse effects of long-term corticosteroid treatment, a family of anti-inflammatory medications known as calcineurin (Cn) antagonists are prescribed. When it comes to the immune response, Cn is crucial. Inflammatory cells contribute to the development and maintenance of atopic dermatitis skin inflammation. T cells, mast cells, basophils, eosinophils, and Langerhans cells (LC) are some of them. T cells are activated as a result of LCs' antigen presentation. Peptide antigens are bound to the high-affinity IgE receptor (FcR1) on the surface of LCs by unbound IgE that has been infiltrated from the inflammatory infiltrate[54]. Individuals with allergy rhinoconjunctivitis who have

specific IgE antibodies to antigens may profit from allergen-specific treatment. The primary goal of this treatment is to create a clinical resistance to the particular allergen; to do this, it lowers periodic rises in allergen-specific IgE while boosting the synthesis of specific IgA and IgG4. A rise in the synthesis of IL-10 and TGF-1 mediates these effects.

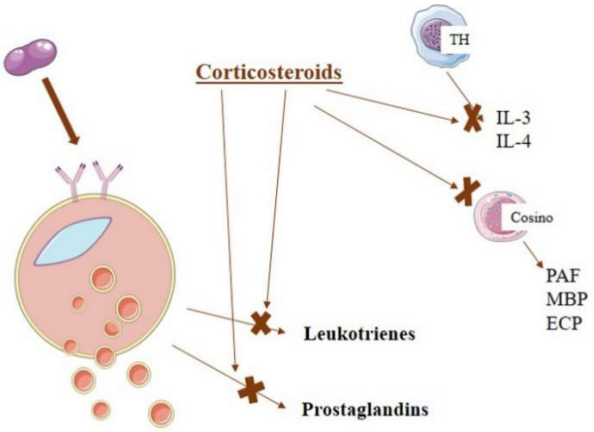

Figure 5. Mechanism of action of corticosteroid.

PAF: platelet-activating factor; MBP: major basic protein; ECP: eosinophilic cationic protein.

6.3 Mast cell stabilizers

Type 1 hypersensitivity reaction is strongly influenced by mast cells. Therefore, mast cell stabilizers play a very important role[55]. Lodoxamide and sodium cromoglicate are mast cell stabilizers that work well in the treatment of moderate allergic responses because they stop neutrophils, eosinophils, monocytes, and mast cells from becoming activated, chemotactic, degranulating, and toxic. Their mechanism of action is shown in **Figure 6**[56]. Because of direct drainage into the nasal mucosa via the nasolacrimal duct, mast cell stabilizers have also been observed to relieve nasal symptoms[57]. It controls the early-phase inflammation of VKC most effectively. Mast cell stabilizers require extended, consistent dosage over many weeks to load for the preventive effect, hence the adoption of sustained drug release methods is important to address the potential problem of patient compliance[58,59].

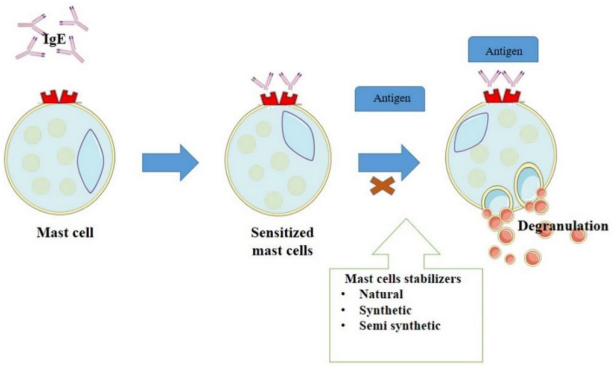

Figure 6. Mechanism of action of mast cell stabilizers.

6.4 Dual action agent

Dual antihistamine topical therapy combined with mast stabilizer use is recommended for AC. In comparison to mast cell stabilizers, topical antihistamines, and dual-acting medications may have provided symptom alleviation more quickly. Epinastine, ketotifen, bepotastine, and azelastine are among those that can be used twice daily; olopatadine and alcaftadine can only be used once daily. The secondary effect is also shown by some of these agents such as cytokine activation and inhibition of eosinophil migration[60,61]. The FDA-approved first topical drug (with dual actions) for the therapy of AC, olopatadine 0.1%, was first made available in

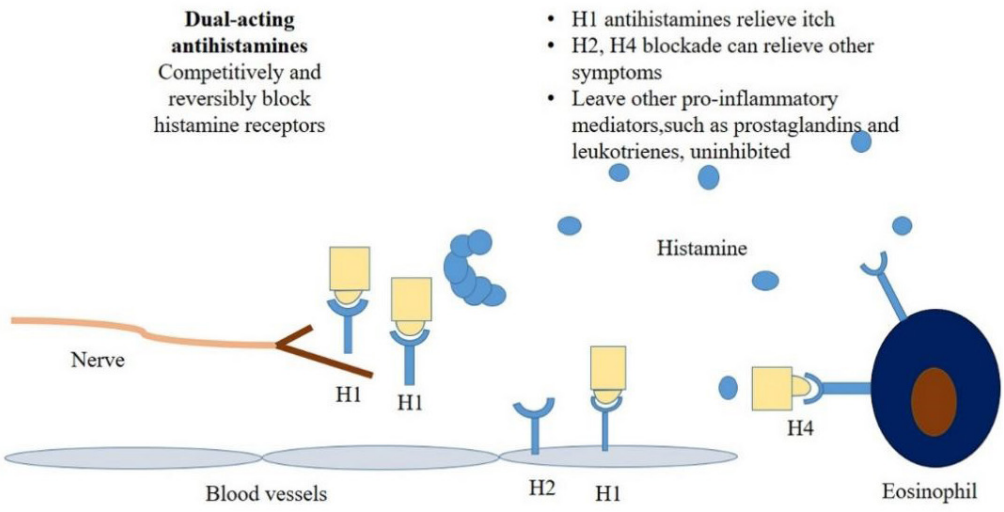

Figure 7. Mechanism of action dual-acting antihistamines.

1996. The newest dual-action drug on the market is alcaftadine which has been authorized for use in AC in 2010. It has been demonstrated that it affects eosinophil recruitment because it has a lesser affinity for H4 receptors than olopatadine and a greater affinity for histamine H1 and H2 receptors (**Figure 7**)[62].

6.5 Non-steroidal anti-inflammatory drug

Topical non-steroidal anti-inflammatory drugs (NSAID) inhibit the production of prostaglandins, which is a factor in IgE-mediated allergic reactions, by blocking the cyclooxygenase pathway. NSAID changes intraocular pressure by inhibiting COX 1 and 2 enzymes (**Figure 8**)[63]. The US Food and Drug Administration (FDA) has licensed certain topical NSAIDs for use in treating ocular atopy, however, the effectiveness of these treatments varies significantly. Although it can instantly alleviate ocular problems, it is typically not recommended and is only to be used temporarily owing to its negative effects, which include corneal melting and eye irritation with continuous usage. It only provides relief in itching not much in any other symptoms. Considering their problematic background, topical NSAIDs have several benefits following intraocular and refractive surgery[64,65].

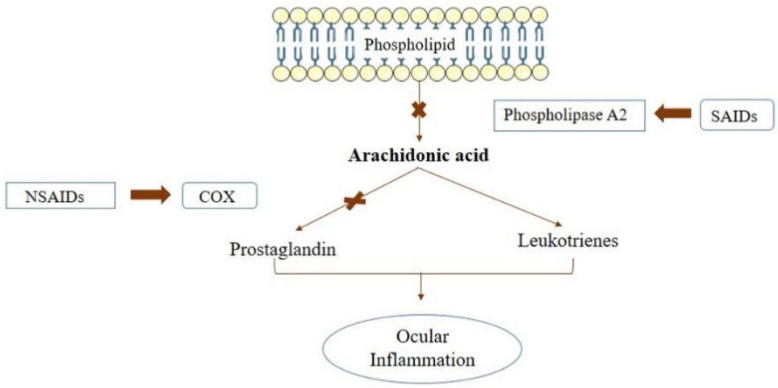

Figure 8. Mechanism of action of NSAIDs.

6.6 Immunomodulators

Tacrolimus and cyclosporine A (CsA) are immunomodulators that inhibit B-cell proliferation, T-helper cell-mediated response, and the release of cytokines and prostaglandins, particularly interleukin (IL)-4, IL-5, and IL-2, which are involved in ocular allergy disorders[66]. It also prevents mast cells from releasing histamine. And is an effective substitute for topical steroids to manage the disorders, especially in cases where they are resistant to other treatments due to its robust anti-inflammatory actions and benign side effect profiles. Although the underlying processes of tacrolimus and cyclosporine A are similar, cyclosporine A has 50–100 times the effectiveness of the latter. As CsA is li-

Table 3. Agents for ophthalmic use

Class of drug	Mechanism of action	Drugs	References
Topical antihistamines	It particularly blocks the histamine receptors.	Emedastine Levocabastine Bilastine	[69,70]
Corticosteroids	Inhibit leukotriene and prostaglandin synthesis.	Hydrocortisone Loteprednol	[71,72]
Mast cell stabilizers	Inhibit the release of histamine and mast cell degranulation.	Lodoxamide Pemirolast	[73,74]
NSAIDs	Inhibit COX 1 and 2 enzymes, thus inhibiting prostaglandins.	Diclofenac Ketorolac	[75]
Dual acting agents	Inhibit histamine release, mast cell degranulation, and block H1 receptor.	Olopatadine Alcaftadine	[76]
Immunomodulators	T cell activation inhibition.	CsA Tacrolimus	[77]

pophilic topical application of it is not easy, so it is dissolved in an alcohol oil base[67,68].

6.7 Immunotherapy

Sublingual immunotherapy (SLIT), a successful treatment for allergy rhinitis, develops an immune system that is unique to allergens. The immunotherapy approach provided by SLIT is easier to administer. Many RCTs assessing the effectiveness of SLIT for allergic rhinoconjunctivitis (ARC) in recent years have focused on the treatment's specific impact on ocular symptoms. In studies, SLIT has shown its efficacy on itchy, gritty eyes, a reduction in watery eyes, and a reduction in red eyes, but there is no significant effect on ocular swelling. So overall, the use of SLIT therapy leads to a reduction in the symptoms of allergic conjunctivitis[78–80].

6.7.1 Intralymphatic immunotherapy

The dose used in this therapy is typically lower and the allergen delivery to lymph nodes is 100 times more than any other route of administration. This therapy is also allergen-specific like SLIT[78]. In a trial, patients were randomly assigned to receive 3 intralymphatic injections spaced out over two months or 54 subcutaneous injections spread over three years in a monocentric, open-label experiment (n = 165). Participants were evaluated using symptom evaluations, skin probe tests, IgE levels, and olfactory stimulation at 3 months, 1 year, and 3 years. Patients in the ILIT group displayed greater resistance to agitation in a nasal area with pollen after 3 months (p = 0.001). These individuals' established a long-lasting tolerance that was akin to SCIT. Less negative events were also recorded by patients in the ILIT arm[81].

7. Patents

Examples of inventive formulations for the therapy of allergic conjunctivitis are provided in **Table 4** over the past ten years.

8. The potential targets for the therapy of allergic conjunctivitis

8.1 Transient receptor membrane potential (TRP) antagonists

The stimulation receptors present on cellular membranes known as transient receptor potentials (TRPs) comprise the vanilloid, canonical, mucolipin, melastatin, and ankyrin classes. In allergic illnesses like allergy eczema and allergic rhinitis, TRP vanilloid (TRPV1) and ankyrin (TRPA1) are both associated with the increase of Th2 activity and associated inflammation[90,91].

8.2 Janus kinase inhibitors

Inhibiting the Janus kinase, which interacts with cytokine receptors, may lessen the cytokine signaling required to cause immune-mediated diseases because cytokines such as IL-4 and IL-5 are essential for the immunopathology of AC[92]. JAK1 and JAK3, which are known to connect to the cytokine receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, are blocked by the new Janus kinase drug tofacitinib. JAK3 inhibition inhibits both the expansion of IL-4-producing Th2 cells and the expansion of the IL-2-stimulated T cells[93].

8.3 Biologics

These medications work better at reducing underlying inflammation. Omalizumab is being tried for AC after showing promising outcomes, especially as a therapy for asthma which does not react well

Table 4. Recent patents for allergic conjunctivitis

Patent No.	Country code	Publication name	Year	References
US 9844530 B1	US	Ophthalmic solutions for glaucoma and conjunctivitis treatment	2017	[82]
US 10426790 B2	US	Treatment of allergic eye conditions with cyclodextrins	2019	[83]
US 20210052488 A1	US	Medicinal preparation and medical instrument	2018	[84]
US 20190151283 A1	US	Non-steroidal selective glucocorticoid receptor agonistic modulators (SEGRAMS) and uses thereof	2019	[85]
US 20220265783 A1	US	Viral conjunctivitis treatment using ranpirnase and/or amphinase	2022	[86]
US 20220370419 A1	US	Drug delivery from hydrogels	2022	[87]
US 20210322457 A1	US	Treatment and diagnosis of ocular surface disorders	2021	[88]
WO 2019135779 A1	WO	Novel ophthalmic composition and method of use	2019	[89]

to oral corticosteroids. Omalizumab is being explored for the subcutaneous injection treatment of AC because of its impact on IgE-mediated illnesses[94].

8.4 Reactive aldehyde species inhibitor

Reproxalap is a topical RASP inhibitor and can be used to treat dry eyes, noninfectious anterior uveitis, and other inflammatory eye diseases. Among other pro-inflammatory signaling molecules, RASP, a well-known pro-inflammatory substance, triggers nuclear factor inflammasomes, kappa B, and prohistaminic factors, increasing inflammation. It accomplishes this by attaching chemically to amino and cysteine groups on receptors and kinases[95]. RASP can result in the activation of inflammasomes and the release of proinflammatory cytokines during periods of inflammation. AC signs and symptoms can be lessened by blocking this process and lowering histamine and inflammatory levels[96].

9. Recent research

Table 5. Recent research for the treatment of allergic conjunctivitis

S. No.	Title	Year	Method	Outcomes	References
1.	Dual inhibition of complement component 5 and leukotriene B4 by topical rVA576 in atopic keratoconjunctivitis	2021	3 patients with moderate or severe AKC who have been getting topical treatment for 3 months have been used in this trial. rVA576 ocular drops were given to patients twice daily for eight weeks.	The eye drops rVA576 responded to the indications and symptoms of ongoing inflammation and have been safely tolerated.	[97]
2.	Randomized study of efficacy and safety of a dexamethasone intracanalicular insert in patients with allergic conjunctivitis	2021	Patients with allergy-related conjunctivitis underwent a 1:1 randomization to receive dexamethasone inserts or control inserts in both eyes, and their condition was evaluated.	Provide relief from itching and reduction in conjunctival redness. Maintained a favorable safety profile.	[98]
3.	Allergy conjunctivitis and the new RASP inhibitor reproxalap: Clinically relevant activity	2021	Subjects with AC were randomly assigned 1:1:1 and given test medicine to compare the effects of two external eye reproxalap doses (0.25 and 0.5%) vs. a vehicle ten minutes before a conjunctival seasonal allergens challenge.	Reduction in ocular itching in patients suffering from AC.	[99]
4.	Efficacy of N-acetyl aspartyl glutamic acid (NAAGA) vs. fluorometholone (FM) for treating AC in an environmental exposure chamber	2022	24 patients with allergic conjunctivitis participated in the trial. Randomly chosen participants have been given either 5 days of therapy with FM followed by NAAGA (n = 12) or NAAGA followed by FM (n = 12). After each treatment, patients in ALYATEC EEC have been exposed to an airborne concentration of Bet v 1.	NAAGA was no less than FM in providing therapeutic relief. Less frequent occurrence of adverse events with NAAGA as compared to that of FM.	[100]
5.	Lirentelimab for severe and chronic forms of AC	2022	30 subjects with severe VKC, AKC, and perennial AC have been given lirentelimab infusion for 6 months.	The signs and symptoms of reactive eyes all appeared to be getting better. Improvement has also been noted for atopic conditions.	[101]
6.	Treatment of ocular allergy itching with antihistamine-releasing contact lenses	2019	Test lenses: Etafilcon A (0.019 mg ketotifen) control lenses: etafilcon A (no drug) 3 groups were made. Group 1 was provided with a test lens in one eye and a control lens in the other eye. Group 3 was given control lenses, whereas test lenses have been given to Group 2 in both eyes.	A reduction in itching and the allergic response was observed.	[102]
7.	Intravenous gold-induced autologous serum injection therapy (Go ACT®) as a novel treatment for seasonal pollen-based allergies	2021	16 patients with proven pollen allergy were involved in this study who haven't shown successful outcomes with the standard medicine.	The treatment has been determined to be efficient, secure, and well-tolerated.	[103]
8.	Formulation and pathohistological analysis of mizolastine-solid lipid nanoparticle-loaded eye hydrogels	2021	The gels have been tested *in vivo* and *in vitro* on a rabbit ocular model of allergic conjunctivitis congestion.	Reduction in AC's signs and symptoms such as inflammation and VEGF and TNF-alpha expression.	[104]

10. Conclusion

AC and other eye allergic diseases are quite widespread, but they are still inadequately recognized and managed. The standard of living can be greatly decreased by AC conditions. Safe and effective therapy choices are therefore crucial. To diagnose AC and rule out alternative explanations, a comprehensive history and physical evaluation are required. There are numerous pharmaceutical choices available, and each patient should receive a personalized treatment plan. Despite the wide range of modern treatments accessible, the signs and symptoms of AC are frequently treated with a combination of drugs. Various new studies are also getting conducted to find the best treatment for this very common problem either by finding the potential targets for the therapy or finding new approaches and most importantly the best therapy. Nanotechnology provides innovative medicinal choices for the treatment of ocular diseases in the future, especially for intractable medication compounds. Upcoming research on the development of nanotechnology drug delivery systems should concentrate on how to achieve acceptable absorption, sustainable release, and dosage precision while avoiding cellular or tissue damage

Conflict of interest

The authors declare no potential conflict of interest.

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