Evolving Concepts In Ocular Allergy

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Allergy is an ancient defence system that was a protective mechanism against parasites. While no one is certain as to why there has been such a surge in its incidence, the fact remains that allergy, including ocular allergy, is on the rise. One theory explaining the increased incidence of allergy suggests that as the background presence of parasites in industrialized countries declined, the immune system developed in such a way that it mistakenly identified trees, grass, weeds, and food as enemies.

Immunologic features of cornea and ocular surface

The immune system of the ocular surface, (cornea and sclera) encompasses features of both the local mucosal microenvironment as well as systemic immunity. The normal uninflamed conjunctival epithelium contains a special subpopulation of dendritic antigen presenting cells known as Langerhans cells (LC). These cells function similar to tissue macrophages elsewhere in the body and serve as the sentinel cells of the immune system on the ocular surface. In addition to the presence of immune cells, conjunctiva has a plentiful supply of lymphatic vessels which facilitate the trafficking of immune cells and antigens to the draining lymph nodes where the adaptive immune response is largely generated.

The normal cornea is also endowed with dendritic cells called Langerhans cells. In the corneal periphery and limbus unlike the corneal centre, these antigen presenting cells are in an activated mature state. Unlike the conjunctiva, normal cornea is considered to be an immunologically privileged site as the generation of immune responsiveness to foreign antigens is relatively suppressed. The important factors responsible for this are the absence of blood vessels and lymphatics, expression of immunosuppressive factors (TGF-â) and Fas-ligand capable for fas mediated apoptosis or programmed cell death by the cornea.

Yoshida et al have found that Langerhan cells bearing IgE in the conjunctiva of atopic dermatitis patients exceed the number found in patients without allergic dermatitis. During an allergic response, Langerhan cells proliferate and migrate to the focus of inflammatory reaction.

Antigens leading to Ocular allergy

Most disorders belonging to the group of ocular allergy are mediated by IgE producing B cells and mast cells (immediate or early phase reactions) as well as T cells (late phase reactions). Antigens leading to rhinoconjunctivitis and allergic keratoconjunctivitis (AKC) are often identifiable by skin testing. Pollen and some microbial agents are important antigens. In Giant papillary conjunctivitis (GPC) the deposits on the surface of contact lenses or probably the contact lens itself may induce a mechanical trauma followed by allergic reaction. In contact allergy, the allergen (drug) binds to a carrier molecule forming the complete antigen being presented to T cells. If vernal keratoconjunctivitis is not associated with atopy, the disease inducing antigen is unknown.
Local Factors

 Conjunctiva has physiologically a more immunosuppressive environment in which CD8+ cells exceed CD4+ cells in the epithelium, exhibiting similar proportions in substantia propria. Mast cells are located in the tarsal and bulbar conjunctiva and in the lid.

Genetic and Environmental factors

In ocular allergy, genetic factors are only known for ocular atopy. The majority of patients with Atopic Keratoconjunctivitis have a family history of atopic dermatitis. For atopic dermatitis, genetic linkage analysis has demonstrated a strong association between IgE reactivity and chromosome 11q. Environmental factors like geographic, climatic, psychologic and occupational seem to be important but are still not well characterized.

B and T cell reaction

Vernal Kerato Conjunctivitis and Atopic Keratoconjunctivitis are mediated by IgE producing B cells and mast cells and by THelper Cell Type 2 (Th2) subgroup of T cells which preferentially activates IgE producing B cells with Interleukin-4 inhibiting the maturation of other B cells. Additionally neutrophils and eosinophils participate in allergic reactions. Eosinophils are activated by mast cells and Th-2 cells and they release cationic proteins stimulating mast cells. Eosinophils also can activate T cells resulting in the perpetuation of the system. For contact allergy, T cell response seems so strong that an early phase reaction may be absent.

Important Immune Mediated Diseases of Ocular Surface

Ocular allergic conditions range from the acute, self limited, mild form of seasonal allergic conjunctivitis to the chronic, severe, sight threatening atopic keratoconjunctivitis. Two acute disorders, seasonal allergic conjunctivitis and perennial allergic conjunctivitis and three chronic diseases, vernal keratoconjunctivitis, atopic keratoconjunctivitis and giant papillary conjunctivitis are described.

Contact Dermatoblepharitis: This may occur acutely as an anaphylactic reaction or have a delayed onset. Anaphylactic reactions are Type 1 IgE mediated hypersensitivity reactions. Contact blepharocconjunctivitis is a Type 4 cell mediated or delayed hypersensitivity reaction that may occur 24-72 hrs following exposure to the sensitizing agent. Medications commonly associated with this entity are cycloplegics like atropine and homatropine, aminoglycosides like neomycin, tobramycin, gentamycin etc, antivirals such as idoxuridine, preservatives such as thiomersal and EDTA.

Atopic Dermatitis: Is a result of increased IgE hypersensitivity.

Hay fever conjunctivitis and Perennial allergic conjunctivitis:

These are largely IgE mediated immediate hypersensitivity reactions. Often these patients suffer from other atopic diseases like asthma, allergic rhinitis etc.

Vernal Keratoconjunctivitis (VKC): The immunopathogenesis appears to involve both type 1 and type 4 hypersensitivity reactions.

Atopic keratoconjunctivitis: These patients demonstrate signs of type 1 immediate hypersensitivity responses but also have depressed systemic cell mediated immunity.

Ligneous conjunctivitis: The cause of this condition is recently linked to severe deficiency in type1 plasminogen, and medical therapy by administration of purified plasminogen concentrate is reported to be effective.

Contact lens induced conjunctivitis: Here the pathogenesis is often multi-factorial. Immune mediated response may result from a variety of insults like allergy, dry eyes, infection, mechanical trauma etc. A hypersensitivity reaction to the contact lens polymer itself or other foreign materials adhering to it has also been postulated. Clinical presentation may vary from mild papillary reaction to giant papillary conjunctivitis.

Pathophysiology

The human eye has approximately 50 million mast cells. Each contains several hundred granules that in turn contain pre-formed chemical mediators. Chronic exposure to antigen result in an antigen IgE antibody
bound to mast cell membrane. The release of a cascade of mediators such as histamine, prostaglandin, leukotrienes and chemotactic factors follows. These mediators cause the itching and hyperemia associated with various forms of allergic conjunctivitis.

The type I and Type IV are the most commonly involved types of allergic reaction involved in ocular allergy.

**Type I Hypersensitivity**

This is the most explosive, immediate and obvious reaction mediated by IgE, mast cells and basophils. It is seen in seasonal allergic conjunctivitis.

**Type IV Hypersensitivity**

Sensitisation occurs when the immune system is first exposed to the antigen. Re-exposure to the same antigen results in delayed reaction (18-72 hours later). This reaction is seen in Vernal Keratoconjunctivitis, Atopic Keratoconjunctivitis, Giant Papillary conjunctivitis (also type I). It is a cell mediated reaction involving T lymphocytes.

The allergic reaction involves an early phase and a late phase reaction.

**Early Phase Response**

In the early phase reaction, an allergen binds to allergen-specific IgE on the mast cell. The mast cell Fc receptors are cross-linked by allergens, sending signals via the cell membrane into the cytoplasm activating the mast cells and resulting in release of allergic mediators. This early phase reaction is immediate.

There are two components of the allergic mediator release from the mast cells. The first is the degranulation of mast cells due to an influx of calcium and a change in membrane permeability of the cell resulting in release of pre-formed mediators including histamine, proteoglycans (tryptase). Eosinophil chemotactic factor is also released. The released histamine binds to H1 and H2 receptors on the conjunctival cell surface. H1 receptor binding results in vasodilation and increased vascular permeability resulting in ocular itching. H2 receptor binding results in increased mucus production at ocular surface.

The second component of mast cell activation is the release of newly synthesized mediators formed via the arachidonic acid cascade.

**Late Phase Reaction**

More severe allergic reactions may demonstrate a late phase reaction. These may be either sustained early
phase reactions or more discrete second peaks of response. The second peak late phase conjunctival reaction occurs from 2 to 9 hours after antigen exposure. This occurs at a cellular level and does not correlate with a separate clinical late-phase response of allergic conjunctivitis.

Usually about 4-6 hours after allergen exposure, an influx occurs into conjunctival tissue of non-specific cells of the inflammatory response, including neutrophils, basophils, eosinophils and T-lymphocytes. The eosinophils and T helper type 2 (TH 2 ) lymphocytes and cytokines are primarily responsible for the later phase reaction.

The infiltration of eosinophils is paramount to the allergic response. Chemotactic factors released during mast-cell degranulation aid in eosinophilic attraction and activation. The eosinophils release toxic proteins such as eosinophil major basic protein (MBP) and eosinophil cationic protein (ECP). These proteins have profound cytotoxic effects and stimulate further degranulation of the mast cell initiating a cascade of allergic events.

The TH2 lymphocytes commonly release cytokines i.e. interleukin 4 (IL-4), IL-5, IL-6 and IL -13 during the late-phase allergic inflammatory reaction.

A recent study now indicates that mast cells may also be a source of TH-2 type cytokines.

The function of mast cells in seasonal allergy conjunctivitis and perennial allergic conjunctivitis is clearly an important one. TH2 type cytokines, an increase in the ratio of TH1/TH2 cytokines and increased adhesion molecules all play a role.

**Management**

The drug treatment options for allergic conjunctivitis have markedly expanded over the last few years, providing opportunities for more focused therapy.

**Non-Pharmacological Intervention**

1. **Identification and avoidance of allergen**

This involves education of the patient and family on the nature of the causative allergies and their environmental control. This includes a) preventive measures against “pollen” like limiting outdoor activities, use of AC or air filter, driving in cars with window closed and with AC or air filter on, using protective eye gear when outdoors (b). measures against mites like effective barrier cover for mattresses and pillows, washing bedding regularly at 60°C (130°F), removing reservoirs of dust eg books, carpets, curtains, upholstery furniture, reducing humidity and vacuuming or damp dusting the entire house weekly; c) measures against animal allergens by eliminating animals from house.

2. **Dilution of antigen**

This can be very effective especially in an acute attack. Rinsing the eyes with luwe warm water, previously boiled and cooled water to which one teaspoon of table salt and half teaspoon of bicarbonate of soda is added will help to wash away the allergen. Alternatively instillation of tear substitutes will dilute the antigen load.

3. **Cryotherapy**

Application of ice to the closed eyelids will help in acute cases to reduce chemosis and eyelid swelling, aid vasoconstriction and relieve itching.

**Pharmacological Intervention:**

1. **Antihistamines**

Abelson et al\(^1\) demonstrated that topical instillation of histamine produced, in a dose dependent fashion, the itching and redness associated with allergic conjunctivitis. Studies have shown that the stimulation of H\(_1\) receptors elicits ocular itching\(^2\) and H\(_2\) receptors produce vasodilatation of conjunctival vessels without itching\(^3\). Histamine is released in the early phase allergic reaction by activation of mast cells and is released in the late phase allergic reaction by mast cells and basophils via activation of histamine releasing factors. By competing with histamines for receptors on effector cells, both H\(_1\) and H\(_2\) antihistamines effectively prevent the immune response and the manifestation of clinical signs and symptoms of allergic disease. In addition to this, many of the available antihistamines also prevent histamine production, bind to adrenergic, cholinergic and muscarinic receptors and inhibit mediator release
from mast cells while others inhibit different components of the allergic inflammatory cascade. Even “pure” antihistamines have some anti-inflammatory action. Inactivation of $H_1$ receptors results in decreased levels of nuclear factor, a transcription factor important in the regulation of cytokine and 1 CAM-1 expression which plays a critical role in the allergic cascade.

**Systemic Antihistamines**

These significantly dampen or block the early phase and some features in the late phase allergic response. They however have a late onset of action compared to topical antihistamines. They also lead to decreased tear secretion and drying of ocular surfaces and may thereby increase the allergen load. Attaining adequate concentration in ocular tissues is difficult. Hence it is generally avoided in ocular allergy unless there are systemic symptoms. Adverse effects include sedation and dryness of secretions. However this is less with the second generation anti-histamines which have selective $H_1$ receptor blockade and less anti-cholinergic effect eg. cetirizine, fexofenadine, loratadine, desloratadine.

**Topical Antihistamines**

Topical ophthalmic preparations of $H_1$ antihistamines currently include an alkylamine (pheniramine maleate), two ethylenediamines (antazoline phosphate and pyrilamine maleate), two piperidines (levocabastine hydrochloride and ketotifen fumarate), a dibenzoxepin (olopatadine hydrochloride) and a benzimidazole (emedastine fumarate). Pheneramine maleate, antazoline phosphate and pyrilamine maleate are only available in combination with vasoconstrictors while the others are available without a vasoconstrictor.

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Composition</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livostin</td>
<td>Janssen-Cilag</td>
<td>Levocabastine</td>
<td>0.05 %</td>
</tr>
<tr>
<td>Albalon-A</td>
<td>Allergan</td>
<td>Antazoline Naphazoline</td>
<td>0.5 % 0.05 %</td>
</tr>
<tr>
<td>Sperallerg</td>
<td>Restan</td>
<td>Tetryzoline Naphazoline</td>
<td>0.04 % 0.05 %</td>
</tr>
<tr>
<td>Patanol</td>
<td>Alcon</td>
<td>Olopatadine</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Emadine</td>
<td>Alcon</td>
<td>Emedastine</td>
<td>0.05 %</td>
</tr>
<tr>
<td>Zaditen</td>
<td>Restan</td>
<td>Ketotifen fumarate</td>
<td>0.025 %</td>
</tr>
<tr>
<td>Relestat</td>
<td>Allergan</td>
<td>Epinastine</td>
<td>0.04%</td>
</tr>
</tbody>
</table>

**Pheniramine (0.3%), Pyrilamine (0.1%) and Antazoline (0.5%):** are classic antihistamines that have been used since the 1940s. The recommended dose is 1 to 2 drops up to four times daily.

The topical antihistamines can further be divided into “pure” antihistamines like levocabastine and “multiple-action” group with combined antihistamine activity, mast cell stabilization and pro-inflammatory mediator action e.g. olopatadine, emedastine, ketotifen, azelastine, epinastine.

**Levocabastine**

This is a pure antihistamine which is long acting and highly potent with a selective $H_1$ receptor antagonist action. It has been shown to down-regulate 1 CAM-1 expression. It is 15,000 times more potent than chlorpheniramine in the rat model. Levocabastine 0.05% has been shown to be effective in reducing itching, hyperemia and chemosis. It is used in a dosage of 4 times daily. It has been shown to be more effective than topical sodium cromoglycate for the treatment of allergic conjunctivorhinitis and as efficacious, well tolerated and possessing a faster onset of action than lodoxamide, another mast cell stabilizer.

**Olopatadine 0.1%** is the first dual action allergy therapy to receive approval as both an antihistamine and a mast cell stabilizer potentially reducing the need for multi-agent therapy. It has been shown to be 1059 times more selective for $H_1$ receptors than for $H_2$ receptors. Its dosing regimen is one drop twice daily.

Olopatadine has been shown to inhibit histamine, tryptase and prostaglandin D$_2$ release from human conjunctival mast cell preparations in vitro. It has been shown to be effective against ocular pruritis up to 8 hours. It is administered twice daily. It has been found to be more efficacious than 2 weeks of nedocromil and oral loratidine. It is well tolerated and can be used in children 2 years and older. The most frequently reported side effects are dry eye, pruritis, stickiness, taste perversion and abnormal dreams.

**Emedastine 0.05%** is a potent selective $H_1$ antagonist with rapid onset and acceptable duration of action. Its selectivity accounts for its low side effects. It has an inhibitory effect on eosinophil chemotaxis. It has been found to be superior to levocabastine and topical nedocromil. It can be used up to four times daily.
Ketotifen 0.05% is one of the more recently approved anti-allergic eye drops. It is a non competitive H₁ receptor and eosinophil inhibitor antagonist. It stabilizes mast cells, inhibits platelet activating action and acts as an eosinophil inhibitor. It has been shown to inhibit the release of leukotrienes, inhibit eosinophil chemotaxis and suppress eosinophil activation by cytokines. It may down-regulate mast cell degranulation to below baseline measurements. A single dose was found to be superior to 2 weeks of nedocromil.

Azelastine: is a relatively selective H₁ receptor antagonist and inhibitor of the release of histamine and other mediators from mast cells. It downregulates 1CAM-1 expression on conjunctival epithelial cells.

Epinastine: The latest “multiple action” topical agent, epinastine, has an H₁ and H₂ receptor antagonist with mast cell stabilizing and anti-inflammatory properties. H₂ receptor antagonism may provide additional benefits in reducing hyperemia and eyelid swelling. Epinastine has a rapid onset of action (3 minutes) and long duration of action (> 8 hours). It has been found to be similar or superior to levocabastine and superior to olopatadine in a small study. Its safety and tolerability appears to be equal to other topical antihistamines.

It has low systemic exposure and does not cross the blood brain barrier.

**Side effects of topical antihistamines**

Some topical antihistamines are contraindicated in patients with narrow angle glaucoma. The mydriatic effect of vasoconstrictors in combination products could precipitate an attack of angle closure. These combinations may also be responsible for the loss of accommodation and the difficulty in near work experienced by some. These combinations should be used with caution in patients with hypertension, cardiovascular disease and poorly controlled diabetes.

Systemic side effects with topical ocular antihistamines are rare. Local irritation, including burning or stinging may occur, which usually resolves within a few seconds after instillation. Keratitis medicamentosa and punctate keratitis may be found associated with the preservative benzalkonium chloride.

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**II. Ophthalmic Vasoconstrictors**

These are used alone or in combination with other agents like antihistamines.

The release of vasoactive amines is responsible for the hyperaemia, tearing and itching that occur with allergic conjunctivitis. Vasodilation results in endothelial gaping, fluid transudation, chemosis and lid oedema. By constricting the blood vessels, vasoconstrictors are able to alleviate these effects.

**Table 2- Topical Adrenergic Medications**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naphazoline</td>
<td>Antistin_Privin</td>
<td>Restan</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Prefrin</td>
<td>Allergan</td>
<td>0.012 %</td>
</tr>
<tr>
<td>Oxymetazoline</td>
<td>Oxylin</td>
<td>Allergan</td>
<td>0.025 %</td>
</tr>
<tr>
<td>Tetrahydrozoline</td>
<td>Gemini</td>
<td>Restan</td>
<td>0.05 %</td>
</tr>
</tbody>
</table>

1. Phenylephrine: This is the oldest of the currently available vasoconstrictor agents.
2. Naphazoline – 0.012 %–0.1 %.
3. Tetrahydrozoline 0.05 %. Use of this drug does not alter pupil size or raise intraocular pressure but rather lowers IOP 30 minutes after use.
4. Oxymetazoline 0.025 %

**Side Effects**

These drugs are readily available over the counter and are hence misused. Prolonged use can lead to rebound vasodilatation due to receptor desensitization. Acute and chronic forms of conjunctivitis by pharmacological, toxic and allergic mechanisms can occur. Hence these products should not be used for prolonged periods.

**III. Mast Cell Stabilizers**

Cromolyn sodium (Opticrom) became the first widely used mast cell stabilizer for the treatment of allergic conjunctivitis, atopic keratoconjunctivitis and vernal keratoconjunctivitis after it was developed in the 1960s from Khelin, an extract derived from the seed of Ammi Visnaga, an Eastern Mediterranean plant used by the ancient Egyptians as an antispasmodic. Subsequently, other mast cell stabilizers like lodoxamide, permirolast, nedocromil, olopatadine and ketotifen have come into the market.
Table 3: Mast Cell Stabilisers

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cromolyn Na</td>
<td>Chromohexal</td>
<td>Hexal</td>
<td>2 %</td>
</tr>
<tr>
<td>Lodoxamide</td>
<td>Alomide</td>
<td>Alcon</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Olopatadine</td>
<td>Patanol</td>
<td>Alcon</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>Ketotifen</td>
<td>Ciba</td>
<td>0.025 %</td>
</tr>
</tbody>
</table>

**Mechanism of action**

Mast cell stabilizers repress type I hypersensitivity reaction by inhibiting the degranulation of mast cells and by preventing the release of histamine and other mediators of hypersensitivity reactions. They have no direct vasoconstrictor, antihistaminic, or anti-inflammatory actions. These actions are reportedly achieved through the prevention of calcium influx into mast cells following antigen stimulation. Hence, once the mediators of inflammation are released these cannot reverse the reaction but can only prevent further mediator release. Olopatadine and ketotifen have both mast cell stabilizing and antihistaminic properties.

**Cromolyn Sodium**

This is beneficial in the treatment of seasonal and perennial allergic conjunctivitis, vernal and atopic keratoconjunctivitis. It is extremely well tolerated in the eye and the risks of long-term use are negligible. Its long safety record (up to 10 years of continuous use) makes it the drug of choice of many clinicians for long-term use. Recommended dosage is 4 to 6 times per day. It may take up to 7 days to obtain relief and a 10 to 14 day period is recommended to evaluate the efficacy of therapy. Side effects include transient ocular burning or stinging on instillation.

**Lodoxamide**

It has been in use since the mid 1990s and has a similar mode of action to cromolyn sodium. It has been shown to be 2500 times more powerful than cromolyn sodium in inhibiting the signs and symptoms of allergic eye disease and to powerfully prevent shield ulcers in Vernal Keratoconjunctivitis. This finding is of particular importance because these changes are typically resistant to treatment. It is a safe drug and can be used 4 times a day for up to 3 months. The onset of action is earlier, the clinical improvement significantly greater and incidence of adverse effects lower than cromolyn sodium. Transient burning, stinging and ocular discomfort were experienced by 15% of patients in clinical trials.

Olopatadine and Ketotifen - have been dealt with along with antihistamines

**Pemirolast:** is thought to be a mast cell stabilizer that inhibit release of phospholipid by products histamine and leukotriene. It may also prevent migration of eosinophils from the blood stream to the site of infection and subsequent release of mediators.

**Nedocromil Sodium**

Nedocromil Sodium appears to be more potent than cromolyn. It has a wider spectrum of potential as an anti-allergic and anti-inflammatory medication. It prevents not only the release of preformed mediators, but also the release of newly generated mast cells. Additionally, it stabilizes both mucosal and connective tissues whereas cromolyn acts only on the connective tissue mast cells. It may be acting on a pathway common to mast cells, eosinophils, epithelial cells and sensory nerves thereby qualifying it as first rate maintenance therapy in the treatment of ocular allergy. In comparison trials with 2% cromolyn, nedocromil was found to be statistically superior in the treatment of seasonal and perennial allergic conjunctivitis by relieving symptoms such as itching, burning, grittiness and tearing that persisted with cromolyn. The significant benefit of nedocromil sodium over cromolyn and lodoxamide is its dosing requirement. It is administered twice daily, rather than 4 to 8 times daily as with other mast cell stabilizers. The onset of action is rapid and the dosage regimen in easily adhered to by patients.

Transient burning, stinging, unusual taste sensation are some of the reported side effects.

**IV Non-Steroidal Anti-inflammatory Drugs (NSAIDS)**

NSAIDS have shown promise in the management of allergic disorders of the eye. They act by blocking prostaglandin biosynthesis by inhibiting the activity of
cyclooxygenase. This enzyme is responsible for the conversion of arachidonic acid to endoperoxides (PGD$_2$) in ocular and non-ocular tissues. Most NSAIDs do not inhibit the formation of eicosanoids such as leukotrienes which also contribute to inflammation as they are formed through the lipoxygenase arm of the arachidonic acid pathway. However certain NSAIDS (Ketoprofen, diclofenac) may have an inhibitory effect on the lipoxygenase pathway. The only NSAID currently approved by the US FDA for relief of itch due to seasonal allergic conjunctivitis is ketorolac tromethamine 0.5%. The recommended dose is 1 drop 4 times a day$^{24}$. This has been found to be effective and well tolerated for alleviating signs and symptoms associated with seasonal allergic conjunctivitis $^{25}$.  

Diclofenac sodium 0.1% has also been found to be effective in relieving ocular signs and symptoms of allergic conjunctivitis comparable to ketorolac$^{26}$. Flurbiprofen 0.03% has also been found to be effective in reducing hyperemia and ocular itching$^{27}$.

Aspirin, piroxicam and indomethacin 1% administered topically have all shown promise as well. Oral aspirin also appears to be useful both as primary and adjunctive therapy for recalcitrant cases of vernal keratoconjunctivitis$^{28}$. Because of the higher doses required (upto 1 gm daily for 6 weeks) the potential side effects of aspirin should be considered before initiating treatment. Suprofen 0.1% has also provided relief in vernal conjunctivitis and contact lens associated giant papillary conjunctivitis.

Side Effects

The most common adverse effect with topical ocular use of NSAIDS is a stinging sensation following application. Oral NSAIDS can result in a variety of complications like gastrointestinal irritation, increased bleeding time, renal failure, drug interaction with hypoglycemic agents, warfarin, methotrexates etc. Its use in pregnancy and lactation is to be avoided as there are no well-controlled studies in these groups to prove their safety.

V. Corticosteroids

The principles of therapeutic use of corticosteroids

1) For most allergic disease, topical administration is the logical choice, although in the hands of the ophthalmologist, supratarsal or subconjunctival depot steroids are often valuable in unresponsive cases.

2) The minimal effective dose for the shortest amount of time to achieve the desired response is the golden rule. In ocular disease, the therapeutic as well as potential side effects that is increased IOP and cataract formation must be monitored by an ophthalmologist at a slit lamp.

3) The choice of steroid and dosage depends on the severity of the allergic response present. “Weaker” steroids like fluorometholone (FML) and medrysone are less likely to result in IOP elevation.

4) Topical therapy should be tapered slowly over several days to weeks because abrupt discontinuation may flare up the allergic response.

Types of Ophthalmic Corticosteroids

1. Prednisolone acetate 1% - is a synthetic analogue of hydrocortisone and is probably the most effective agent in anterior segment inflammation. However, it is seldom used in ocular allergy.

2. Dexamethasone 0.1% - is 25 times as potent as hydrocortisone.

3. Flurometholone 0.1% – is a structural analogue of progesterone. It is very effective in reducing ocular surface inflammation with a low potential for IOP elevation.

4. Medrysone 1% - is another synthetic derivative of progesterone. It is the least potent and does not produce rise in IOP.

5. Loteprednol etabonate 0.2% - Represents “a soft drug” designed to maximize therapeutic effect while minimizing side-effects. It has proved to be very effective in the treatment of allergic conjunctivitis$^{29}$.

6. Rimexolone 1% - is a novel synthetic topical corticosteroid which possesses similar anti inflammatory effect as prednisolone and no greater associated increase in the risk of elevating IOP than fluorometholone $^{30}$. It has limited systemic absorption contributing to the clinical safety of the product.
Side Effects

As steroid dosage and duration increases, the side effects also increase.

Both systemic and topical steroids result in increased lens opacities usually posterior sub capsular cataracts. This can result in photophobia, glare and decreased vision.

Topical steroids can also cause elevation of IOP especially in steroid responders which is usually reversible. Those with glaucoma, family history of glaucoma, myopia > 5 D, patient age, Krukenberg spindles and diabetes are more prone to raised IOP. Dexamethasone 0.1 % and betamethasone 0.1 % are more likely to induce pressure elevations than prednisolone, fluoromethalone and medrysone. Fluoromethalone has less tendency while medrysone has the least tendency to elevate IOP.

Resistance to infections is lowered with increased risk of developing viral, bacterial and fungal infections. Corneal healing is delayed. Anterior uveitis can occur. Dilation of pupil and ptosis can occur. Temporary ocular discomfort following topical ocular administration can occur. Additionally occasional refractive changes, blurred vision, increase in corneal thickness, dry eye and calcium deposits on cornea have been reported. Systemic side effects are infrequent.

Table 4. Types of ophthalmic corticosteroids

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Trade Name</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prednisolone</td>
<td>Minims Pred</td>
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</tr>
<tr>
<td>Phosphate</td>
<td>Sodium Phosphate</td>
<td></td>
</tr>
<tr>
<td>2. Prednisolone</td>
<td>Pred Mild</td>
<td>0.12 %</td>
</tr>
<tr>
<td>acetate</td>
<td>Pred Forte</td>
<td>1 %</td>
</tr>
<tr>
<td>3. Dexamethasone</td>
<td>Maxidex/</td>
<td>0.1 %</td>
</tr>
<tr>
<td>Suspension</td>
<td>Spersadex</td>
<td></td>
</tr>
<tr>
<td>4. Dexamethasone</td>
<td>Decadron</td>
<td>0.05 %</td>
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<tr>
<td>Ointment</td>
<td>AK-Dex</td>
<td></td>
</tr>
<tr>
<td>5. Fluoromethalone</td>
<td>Flucin</td>
<td>0.1 %</td>
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<tr>
<td>Suspension</td>
<td>FML Forte</td>
<td>0.1 %</td>
</tr>
<tr>
<td>FML</td>
<td>0.25 %</td>
<td></td>
</tr>
<tr>
<td>6. Fluoromethalone</td>
<td>FML SOP</td>
<td>0.1 %</td>
</tr>
<tr>
<td>ointment</td>
<td>HMS</td>
<td>1.9 %</td>
</tr>
<tr>
<td>7. Medrysone</td>
<td>Vexol</td>
<td>1 %</td>
</tr>
<tr>
<td>Suspension</td>
<td>Lotepred</td>
<td>0.2 %</td>
</tr>
<tr>
<td>8. Rimexolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Loteprednol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Contraindications

Corticosteroids should always be used with caution because of its potential side effects. Caution is needed in patients with diabetes mellitus, infections, congestive heart failure, chronic renal failure or systemic hypertension. Topical steroids must be used only when necessary and with caution in patients with glaucoma. While treating with steroids the patient should be examined for the development of corneal, lens and IOP changes and keratitis.

The step-care management approach to allergic conjunctivitis is recommended

Table 5: Step- Care management of allergic conjunctivitis

<table>
<thead>
<tr>
<th>Topical Cyclosporine A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical Steroids</td>
</tr>
<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Mast cell stabilisers/multiple action molecules</td>
</tr>
<tr>
<td>Antihistamines (Topical/ Systemic)</td>
</tr>
<tr>
<td>Vasoconstrictors</td>
</tr>
<tr>
<td>Ice packs</td>
</tr>
<tr>
<td>Avoidance (e.g. Contact Lenses, Drops/Benzalkonium Cl)</td>
</tr>
</tbody>
</table>

Educating the patients to understand the condition and supplying the patient with all the step care knowledge will aid him or her in controlling symptoms adequately and will therefore reduce depending on drug therapy.

Drugs currently in the Pipeline

Immunomodulatory strategies are being studied

1. These include cyclosporine and tacrolimus which block mast cell proliferation and also may block other cytokines from being released by T lymphocytes. In the future there might be a role for topical cyclosporine in the treatment of severe allergic conjunctivitis. In several small trials, it has been found to be well tolerated and effective in the therapy of allergic and vernal keratoconjunctivitis. Currently topical cyclosporine
is approved by the US FDA for only increased tear production in dry eye patients. At present, the role of topical cyclosporine as a steroid sparing agent in treatment of ocular allergy has not been fully investigated.

2. Anti IgE class of treatments:
IgE plays a crucial role in triggering the allergic reaction, when it binds to the surface of mast cells and other immune cells. In this position it is a sitting duck to which allergens adheres, cross linking the IgE molecules and thereby triggering mast cell degradation and the release of numerous pro-allergy mediators. Thus blocking IgE presents an opportunity for drug intervention. One drug in this class is omalizumab, which acts by binding to free circulating IgE thereby inactivating it. Subcutaneous omalizumab is currently indicated for moderate to severe persistent asthma uncontrolled with corticosteroids. It may become applicable for rare, severe forms of intraocular allergy such as atopic keratoconjunctivitis.

3. Lipoxygenase inhibitors and chemokine inhibitors
These are approaches to controlling the ocular allergic response at specific points in the immune system reaction of allergic conjunctivitis.

Conclusion
The armamentarium against ocular allergy has continued to expand in recent years with introduction of newer agents which are highly potent. A better understanding of these drugs will help to offer an effective and safe treatment regimen for all ocular allergy patients.

References
17. Greiner JV, Michaelson C et al. Single dose of ketotifin
fumarate 0.025 % Vs 2 weeks of cromolyn sodium 4 % for allergic conjunctivitis. Adv Ther 2002 Jul –Aug 19(4):185-93.


