

Allergic conjunctivitis: The evolution of therapeutic options

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ABSTRACT

The eye has become the target of intense pharmacologic development because it represents one of the most active sites of allergic inflammation, due to it having no mechanical barrier to prevent the impact of allergens such as pollen on its surface. Over the past 20 years, we have witnessed an astonishing growth in therapeutic advances, ranging essentially from derivatives of simple aspirin to various newly developed biological immunomodulatory agents, using implantable drug delivery devices that exceed the safety and efficacy of those available for other organ systems and resorting to advanced surgical techniques for the correction of sight-threatening, disease-related complications. Overall, with the expanding knowledge base, the intricacy of ocular inflammation appears to be becoming ever more manageable and the clinical allergist/immunologist has an increasing role in the treatment outcomes of patients with anterior inflammatory disorders of the ocular surface primarily allergic conjunctivitis but also including dry eye syndromes.

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Although the most common form of allergic eye disease has been originally reported to be seasonal and or intermittent allergic conjunctivitis that had been reported to be 90% while the perennial form was only 5%,¹ either there has been a change in the prevalence of these individual conditions or the original report definition of seasonal and perennial forms have changed. Presently, persistent ocular symptoms associated with allergy may be as prevalent as 40% of the population with positive skin tests to various aeroallergens.² Further evidence as to the severity of these conditions is reflected in several of the studies evaluating the impact of intranasal steroids on symptoms of ocular allergy,³ where the impact of intranasal steroid is noted more on seasonal than perennial forms of allergic conjunctivitis. Although the signs and symptoms of seasonal and perennial allergic conjunctivitis are relatively mild to moderate, the impact of allergic eye disease and quality of life can be quite profound by affecting daily activities, productivity at work, and performance in school, resulting in an economic toll on the society.^{4–6} Complications of untreated forms of allergic conjunctivitis are potentially caused by the chronic inflammatory changes at the epithelial surface such as a breakdown of the epithelial cell tight junctions leading to increased allergen penetration,⁷ thus generating a vicious cycle allergen activation of mast cells with eosinophil infiltration leading to release of

mediators such as major basic protein that causes further epithelial defects.^{8–10}

EARLY ENVIRONMENTAL OCULAR ALLERGY TREATMENT

The cornerstone for the treatment of all allergic responses has been focused on decreasing exposure—"environmental." Similarly, some of the earliest reports in the United States of fresh air treatments for allergies comes from a description by Dr. Morrill Wyman who delivered clinical lectures at Harvard on "hay fever" and then published his perspectives in a text where he proposes pollen as the causative agent of "autumnal catarrh."¹¹ He specifically described the effects of Roman wormwood, a member of the same botanical family as ragweed, and noted the relative absence of "hay fever" in the White Mountains of New Hampshire. Thus, he designed an experiment in which he gathered some Roman wormwood in full flower in Cambridge, MA, and packed it for 3 weeks on his way to vacation in the White Mountain Glen refuge. It was then opened after 3 weeks in the mountains and was "sniffed by myself and my son." They both developed sneezing; itching of nose, eyes, and throat; stuffy nostrils; and swollen uvula, without cough; the troubles continued through the night and did not disappear until the following afternoon. Eight persons sniffed the plant: one was "seized with asthma" and did not recover until the next day, one was attacked by catarrh with eyes being involved for several hours, one had sneezing and coughing, two had sneezing only, one had sneezing and watery eyes, one had irritation of the eyes, and one had no symptoms at all. Another 8 people on the same trip who had the same disease, but did not "sniff" the plant, did not suffer from any symptoms. Thus, the continued recommendation of resorts

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in the mountains and seashore-based “retreats” have persisted to this day for those suffering from allergies.

Soon thereafter, experiments by von Pirquet, being awarded the first Nobel Prize in medicine for the development of the antidiphtheria horse serum treatment, subsequently led to the study of serum sickness and anaphylaxis as a consequence of reactions to the horse serum. The term “allergy” was coined with the concept of desensitization to the foreign entity; thus, in 1911, immunotherapy was prescribed as the primary treatment of allergies, spring “catarrh,” before the advent of the chemical pharmaceutical era. In the original report, allergen immunotherapy “measured the patient’s resistance during experiments of pollen extracts to excite a *conjunctival* reaction” with the eye and not the skin as the primary target organ.¹² In addition, the premedication era had a plethora of home remedies that involved the use of herbs and the general pharmacognosy such as the classic use of a tea bag with its astringent property of tannins that are also found in the witch hazel plant as a potential explanation for anti-inflammatory effects.¹³ Traditionally, native North Americans commonly used witch hazel, its leaves known to contain ~7–10% of tannins, as a treatment for eye inflammations.¹⁴ Parallel to the early development of immunotherapy, Hahnemann began compiling his findings, *similia similibus curentur*, the Latin phrase meaning “let likes be cured by likes,” which is the primary principle of homeopathy and noted that *Euphrasia*, *Pulsatilla*, *Belladonna*, and *Apis mellifica* were homeopathic treatments for conjunctivitis, although very few studies have examined the effectiveness of specific homeopathic therapies that had established any clinical effect on conjunctivitis. However, some of these herbal agents such as *Euphrasia officinalis*, *Petasites hybridus*, and *Argemone mexicana* have shown limited impact in more recent studies using more conventional doses and has taken a place in the realm of complementary and alternative medicine.¹⁵

THE ERA OF THERAPEUTICS IN ALLERGY TREATMENT

The era of therapeutics for ocular allergy starts with antihistamines that were the first “pharmacologic” agents to be a primary treatment for allergy and would be used in various formulations to treat allergies including allergic conjunctivitis. In 1937 H₁-antihistamines (H₁-blockers or H₁-receptor antagonists) were discovered by Bovet and Staub at the Institute Pasteur. Several years later in 1942, phenbenzamine (Antergan) was developed and used in the treatment of allergic disease. Within several years, three other antihistamines were synthesized: in 1944, pyrilamine maleate; in 1946, diphenhydramine; and in 1946, triphenlenamine. Interestingly, in 1952, the first antihistamine

eye drop in the United States was developed by an early allergy pharmaceutical company, Allergan, from the same drug used to manufacture an antihistamine nasal drop (originally developed in 1950), “neoantergan,” also known as mepyramine or pyrilamine, that was thought to be a better antihistamine than diphenhydramine. It was an ophthalmologist who recommended that the nasal drop be considered as an eye drop called “Allergan.”¹⁶

The first-generation H₁-antagonists bind to the receptor in a competitive manner and thus with higher doses of histamine they are readily reversible. However, higher doses are associated with increased incidence and severity of side effects. Second-generation H₁-antihistamines bind in a noncompetitive manner and dissociate slowly from the receptor site. In general, topical intranasal or ophthalmic H₁-antihistamines logically have a more rapid onset of action than oral H₁-antihistamines, but they generally require administration several times a day because of washout from the nasal mucosa or conjunctivae.¹⁷

Ocular Decongestants

As early as 1958, ocular decongestants became a common adjunct in the treatment of allergic conjunctivitis¹⁸ with various families of agents that were evaluated that included imidazoles and naphthalenes.¹⁹ The vasoconstrictors xylometazoline and naphazoline are sympathomimetics (adrenergic agonist), which stimulate adrenergic receptors causing capillary constriction and reduced blood flow and therefore reduce hyperemia, chemosis, and eyelid swelling.²⁰ Because topical decongestants primarily act as vasoconstrictors that are highly effective in reducing the erythema, they became widely used in combination with topical antihistamines, but alone had minimal effect on diminishing the allergic response. Few studies have been performed that compare the commercially ocular decongestants. In 1980, in separate studies, the decongestant naphazoline caused significant whitening (but did not prevent itching) of a histamine-challenged eye resulting in a red and itchy eye; although the antihistamine antazoline inhibited itching, it did not reduce redness in the same histamine-induced ocular allergy model. The combination of naphazoline and antazoline produced significant whitening and inhibition of itching in all eyes challenged by histamine, which was more effective than either component alone in preventing redness itching.²¹

In 1984 reports of testing some of the decongestants against each other, naphazoline apparently produced significantly more whitening than did tetrahydrozoline.²² Oxymetazoline (Ocuclear; Schering Merck, Kenilworth, NJ) was thought to have a faster onset of action, longer duration of action, and better deconges-

tant effect than naphazoline (Vasocon; Novartis Ophthalmics, Florham Park, NJ) and tetrahydrozoline (Visine; McNeil, Fort Washington, PA).^{23,24} Additional studies in 1983 noted that the combinations of naphazoline hydrochloride and an antihistamine antazoline phosphate or pheniramine maleate vary greatly in patient comfort and acceptability but were not different in their ability to ameliorate the itching, tearing, redness, and edema.²⁵ Patients using topical ophthalmic decongestant (vasoconstricting) solutions should discontinue the drug if ocular pain or visual changes occur, they experience continued ocular redness or irritation, or the condition worsens or persists for >72 hours.

Although studies have shown that antihistamine-vasoconstrictor combinations are more effective than either alone,^{21,26} long-term use is not recommended, owing to potential adverse effects such as rebound hyperemia. The rebound effect was not reported in short-term use (<10 days), but chronic use of these agents does cause "rebound conjunctivitis."²⁷ They are contraindicated in those with narrow anterior chamber angles because the sympathomimetic vasoconstrictor component exhibits the anticholinergic effect of mydriasis. In addition, they should be used with caution in those with heart disease, high blood pressure, and diabetes because of potential systemic absorption.

Ocular Allergy Treatment Reborn—1990s

Advances in pharmacotherapy for ocular allergy were minimal for 30 years when research started to investigate the conjunctival surface as another form of an immunologically active "associated lymphoid tissue" and new products started to reappear to address the need for better ocular treatment in the 1990s with progressive new treatments and concepts of inflammatory disorders of the ocular surface that not only includes allergic conjunctivitis, but also includes dry eye syndrome. The new topical agents for the treatment of allergic conjunctivitis included a nonsteroidal anti-inflammatory agent, ketorolac; various antihistamines, emedastine and levocabastine; mast cell stabilizing agents, cromolyn, lodoxamide, nedocromil, and pemirolast; dual action agents, olopatadine, ketotifen, azelastine, epinastine, bepotastine, and alcaftadine; topical steroids, loteprednol; and immunotherapy, subcutaneous. On the horizon are new modalities and agents such as selective glucocorticoid receptor agonist (SEGRA), other immunotherapy modalities, and approved use of cyclosporine for dry eye syndromes.

Ketorolac tromethamine (Acular; Allergan, Irvine, CA) is one of the earliest prescription products for the treatment of itch associated with allergic conjunctivitis that was approved in November of 1992. Clinical studies have shown that topical nonsteroidal anti-inflam-

matory drugs significantly diminish the ocular itching and conjunctival hyperemia associated with seasonal antigen-induced allergic conjunctivitis,²⁸ but these agents, unlike topical corticosteroids, do not mask ocular infections, affect wound healing, increase intraocular pressure (IOP), or contribute to cataract formation. A recent study was done on measles conjunctivitis in which it assisted in decreasing the amount of hyperemia and was not associated with any viral spread.²⁹ Ketorolac has been studied in comparison with topical antihistamines with better outcomes in some cases.^{30–33} A common adverse effect is stinging or burning of eyes when medicine is applied. Use 1 drop in each eye four times a day for up to 1 week.

Antihistamines such as levocabastine (Livostin; Novartis Ophthalmics) were introduced in the spring of 1994 for the treatment of allergic conjunctivitis. *In vitro* studies indicated the high selective binding affinity of levocabastine for histamine H₁-receptors along with its exceptionally slow rate of dissociation from these receptors.³⁴ In an ocular provocation study, 10 of 11 patients treated with levocabastine required a 10-fold increase in allergen to reproduce the same symptoms. The pretreatment with an antihistamine did cause an increase in late-phase symptoms in 3 of the 11 patients.³⁵

Emedastine (Emadine; Alcon, Ft. Worth, TX), a relatively selective histamine H₁-antagonist, with no apparent effect on adrenergic, dopaminergic, or serotonin receptors,³⁶ had a concentration-dependent inhibition of histamine-induced vascular permeability. Comparisons of relative potency 30 minutes postdosing between emedastine and other antihistamines indicated that emedastine is equipotent to ketotifen, and more potent than brompheniramine (7×), chlorpheniramine (7×), clemastine (10×), pyrilamine (10×), levocabastine (100×), pheniramine (357×), diphenhydramine (3333×), and antazoline (5813×).^{37,38}

The classic mast cell-stabilizing agent was cromolyn sodium ophthalmic solution (Crolom; Bausch & Lomb, Madison, NJ) that was approved for chronic allergic ocular disorders, including vernal keratoconjunctivitis and giant papillary conjunctivitis. Ophthalmic administration of cromolyn generally provides symptomatic relief of itching, tearing, redness, and discharge within a few days after initiation of therapy; however, up to 6 weeks of therapy may be required for optimum symptomatic relief in some patients. It was never approved for use in allergic conjunctivitis although a study did show some efficacy.³⁹

This impracticality led to the development of additional mast cell stabilizing such as lodoxamide, which was reported to be ~2500 times more potent than cromolyn in the prevention of histamine release in several animal models^{40,41} and has been shown to deliver greater and earlier relief in patients with the more chronic forms of conjunctivitis (*i.e.*, vernal keratocon-

junctivitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis) than cromolyn.^{42,43} However, in a study of allergic conjunctivitis it was only perceived by the patient to be clinically better than that perceived by the physician. Although the development of another cromolyn derivative, nedocromil (Alocril; Allergan), showed a safety profile similar to that of sodium cromoglycate, with increased potency, given just b.i.d., in alleviating the signs and symptoms of seasonal allergic conjunctivitis and provided relief in 80% of patients.⁴⁴ Interestingly, nedocromil was originally thought to be just a mast cell-stabilizing agent but was found to have multiple actions⁴⁵ including H₁-antagonism and inhibitory effects on mast cells and eosinophils.⁴⁶ Nedocromil is associated with stinging or burning of the eyes on application of the drops and a distinctive taste in 5% of the population.⁴⁷ The dual action was something the industry pursued in future pharmaceutical agents. In 1991, pemirolast potassium was being marketed as a tablet formulation in Japan for the treatment of bronchial asthma and allergic rhinitis (AR) because it showed to be specific inhibitor of mast cell degranulation. Its potency is >100 times that of cromoglycate. In a placebo-controlled study evaluating pemirolast 0.1% q.i.d., it was significantly superior to placebo in relieving conjunctival allergen challenge-induced ocular itching.⁴⁸ Furthering the pursuit of agents with multiple actions, the one experiment showed that the simultaneous administration of levocabastine and pemirolast significantly decreased histamine content when compared with either levocabastine or pemirolast alone.⁴⁹

THE ERA OF DUAL-ACTION/MULTIPLE-ACTION ANTIHISTAMINE AGENTS

Thus, the search for newer ophthalmic agents generated an interest in those that may have more than one effect, *i.e.*, a dual effect in inhibiting mast cell activation and blocking the major mediator of ocular, appreciated at the time, histamine.

Ketotifen

Ketotifen (originally marketed as a prescription product, Zaditor [Alcon] and now as Alaway [Bausch & Lomb] as an over-the-counter [OTC] product), has recently become generic and migrated to OTC availability for the treatment of allergic conjunctivitis. Ketotifen is distinguished from the chromones, sodium cromoglycate and nedocromil, by a conjoint mast cell stabilizing, several antimediator properties including strong H₁-receptor antagonism^{20,50} and inhibition of leukotriene formation.⁵¹ Seasonal allergic conjunctivitis patients randomly assigned to one of three groups with either topical ketotifen 0.025% ophthalmic solution, olopatadine 0.1% ophthalmic solution, or placebo, 2 drops per eye b.i.d. for 30 days

showed noted significant improvements of clinical scores (tearing and itching) and reduction in the expression rates of cell adhesion molecules and inflammatory markers in conjunctival surface cells over the course of the month.⁵² Ketotifen has been reported in several studies to have a mild stinging effect on the conjunctival surface and thus compliance may be an issue, but it is presently OTC and is considered first-line therapy.⁵³

Olopatadine

Olopatadine hydrochloride is a relatively selective histamine H₁-receptor antagonist having mast cell-stabilizing features.^{54,55} It is available in two formulations (Patanol 0.1% and Pataday 0.2%; Alcon). Olopatadine has shown inhibition of various cytokines⁵⁶ including TNF- α mediator release from human conjunctival mast cells.^{38,57,58} In one of the few comparative studies of ophthalmic agents, olopatadine fared slightly better than ketotifen in the short course of treatment over 2 weeks.⁵³ In a conjunctival provocation model, comparing olopatadine with azelastine and placebo, olopatadine and azelastine treatments were significantly more effective than placebo in reducing itching postchallenge with olopatadine was more effective than azelastine in reducing itching at 3.5–20 minutes postchallenge.⁵⁹ The original olopatadine was approved for all signs and symptoms of allergic conjunctivitis, whereas the once-a-day formulation is only approved for itching like all the other ophthalmic dual-action agents. Some of these agents have been shown to have a serendipitous impact on nasal symptoms *via* its application down the nasolacrimal duct, which has led to several of these ophthalmic agents being used as intranasal treatment for AR.⁶⁰

Azelastine

Azelastine (Optivar; Meda, Somerset, NJ), originally a second-generation H₁-receptor antagonist that is primarily administered intranasally,^{61,62} had a secondary entry in the topical treatment of allergic conjunctivitis.^{20,63} It appears to have a multiple action by inhibiting histamine release from rat mast cells after antigen and nonantigen stimuli^{64–66} by exerting an inhibitory effect on the IgE secretion⁶⁷ and the down-regulation of intracellular adhesion molecule 1 expression during early and late-phase responses supporting the prophylactic properties of azelastine.⁶⁸ In a study, azelastine was instilled into the eyes of rhinoconjunctivitis patients sensitive to *Parietaria judaica* both before and after antigen-specific conjunctival challenge. Total symptom scores were significantly reduced for up to 6 hours in those patients who were treated topically b.i.d. with azelastine as opposed to placebo for 1 week, accompanied by a significant reduction in conjunctival inflammatory cell infiltration.⁶⁸

Epinastine

Epinastine (Elestat; Allergan), having histamine H₁- and H₂-receptor antagonists with mast cell stabilizing and other anti-inflammatory activities⁶⁹ have shown significant reduction in histamine, TNF- α , as well as some alterations in IL-5, IL-8, IL-10, and TNF- β profiles that were differentially decreased. The agents appear to have slightly different impacts on various parameters such as epinastine-reduced neutrophils influx and other compounds have more of an impact on eosinophils.⁷⁰ Therapy with epinastine has been shown to be safe and effective for at least 8 weeks, with no evidence of tachyphylaxis. In a recent review ketotifen, pyrillamine, and epinastine appeared to have the strongest H₁- and H₂-affinities although a specific clinical study determining the clinical relevance still has to be performed.⁵⁰

Bepotastine

Bepotastine besilate (Bepreve; Ista, Irvine, CA) is a histamine H₁-receptor antagonist with mast cell-stabilizing activity that has also shown inhibition of eosinophil migration to and activation at inflammatory sites.⁷¹ After administration of 1 drop of a 1 or 1.5% ophthalmic solution to both eyes q.i.d. for 7 days, peak bepotastine plasma concentrations occurred 1–2 hours after instillation.⁷² Clinical efficacy of bepotastine besilate was evaluated in two randomized, double-blind, placebo-controlled conjunctival allergen challenge studies in 237 adults and pediatric patients ≥ 10 years of age with a history of allergic conjunctivitis; the 1.5% relieved ocular itching but not conjunctival hyperemia, induced.⁷³ The safety of bepotastine besilate 1.5% ophthalmic solution (administered b.i.d.) was evaluated in a multicenter, randomized double-blind, placebo-controlled clinical study of 861 healthy individuals (including 127 healthy children 3–9 years of age) over a period of 6 weeks. No adverse ocular effects or serious adverse events were reported. The only adverse event reported on a consistent basis is taste in 10–20% of those tested.

Alcaftadine

Alcaftadine (Lastacast; Allergan), a potent H₁-histamine with additional properties of an H₂- and H₄-receptor antagonist, has also shown anti-inflammatory properties such as decreased chemotaxis and activation of eosinophils. Efficacy of alcaftadine for this use has been shown in several controlled conjunctival antigen challenge studies in patients ≥ 10 years of age with allergic conjunctivitis. No difference was noted between the 0.1 and 0.25% when compared with placebo and in one of the few head-to-head studies performed using the ophthalmic agents in the treatment of allergic conjunctivitis, alcaftadine in the highest con-

centration of 0.25% showed similar impact as olopatadine 1% solution.⁷⁴ Alcaftadine appears rapidly in systemic circulation after topical application to the eye, peaking at a median of 15 minutes (active drug) and at 1 hour (carboxylic acid metabolite), and falling to below the limit of quantitation by 3 and 12 hours, respectively.⁷⁵ In a conjunctival allergen challenge animal model of epithelial integrity, alcaftadine protected the epithelial tight junctions, thus, theoretically further decreasing allergen penetration while the olopatadine permitted the disruption of the epithelial tight junctions.⁷

Because all of the topical antihistamines are also known to potentially have muscarinic binding and thus may theoretically exacerbate dry eye syndrome complaints with chronic use, their chronic use needs to be monitored or changed to topical agents. In a study comparing loratadine and epinastine, after treatment of 4 days, loratadine was associated with clinical signs of ocular dryness, including decreased tear volume and tear flow and topical epinastine did not.⁷⁶ In a longer (1 month) head to head in botulinum toxin b murine model for dry eye study of olopatadine and epinastine, no difference was noted⁷⁷ but in another animal model epinastine was found superior.⁷⁸ Thus, the chronic use of ophthalmic eye drops also throws a suspicion of changes in tear film and needs to be monitored.

OPHTHALMIC CORTICOSTEROIDS

Ophthalmic corticosteroids are appropriate for treating severe allergic conjunctivitis because of their potent anti-inflammatory effect; corticosteroids block most inflammatory pathways in the allergic reaction, especially the late-phase mediators that perpetuate the persistent and chronic forms of ocular allergy.^{79,80}

Loteprednol

Loteprednol etabonate (Alrex; Bausch & Lomb) 0.2% ophthalmic suspension is used for the symptomatic relief of seasonal allergic (hay fever and pollinosis) conjunctivitis.^{81,82} Loteprednol etabonate 0.5% ophthalmic suspension also is used for the symptomatic relief of allergic conjunctivitis. Loteprednol etabonate differs structurally from other corticosteroids (*e.g.*, hydrocortisone and prednisolone) by the absence of a ketone group at position C-20 and the presence of an ethylcarbonate ester and a chloromethyl carboxylate group at positions 17- α and 17- β in the steroid nucleus, respectively.^{83,84} Esterification of the hydroxyl group at position 17- α and introduction of a chloromethyl carboxylate group at position 17- β resulted in a compound that is rapidly hydrolyzed in ocular tissues to an inactive metabolite, with a resultant decreased potential for adverse effects (*e.g.*, increase in IOP) com-

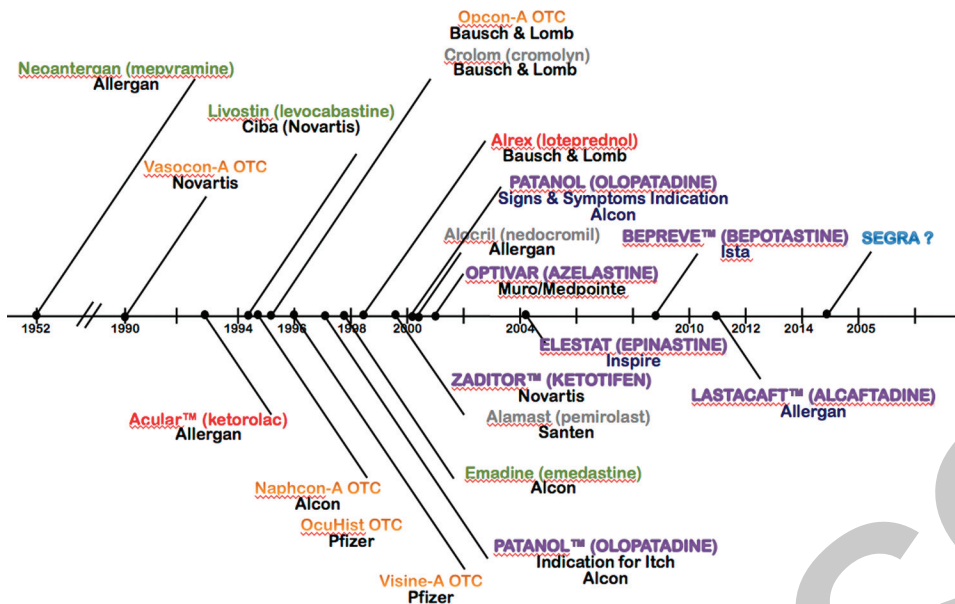


Figure 1. The timeline of ocular allergy agents. The listing of actual agents and their approval years are reflected in the figure with different colors reflecting the type of ophthalmic agents: orange, combination of vasoconstrictor and antihistamine; purple, dual (multiple) action; green, antihistamine; red, nonsteroidal and steroidal compounds; grey, mast cell stabilizing; and blue, future development. SEGAs, selective glucocorticoid receptor agonists.

monly associated with topical ophthalmic corticosteroids. Topical corticosteroids do have the potential to induce serious side effects, such as cataracts, elevated IOP, and infection. Therefore, topical corticosteroids are best used over short periods of time (up to 2 weeks), and for use beyond 2 weeks, IOP and lens clarity should be monitored. They should not be used in conjunction with an a topical antibiotic because if one is concerned about an infection then one has to be concerned that it may be viral, and topical steroids would be contraindicated unless examined by an eye care specialist with a biomicroscope.

Intranasal Steroids

There is a growing body of evidence supporting the effect of intranasal corticosteroids on reducing ocular symptoms associated with AR. Initial evidence for this therapeutic benefit surfaced during placebo-controlled clinical trials of the effects of intranasal corticosteroids on a spectrum of AR symptoms.^{85–87} With more recent studies being more closely examined, it appears that intranasal steroids may be a class effect on ocular allergy because triamcinolone,⁸⁸ beclomethasone,⁸⁹ budesonide,⁹⁰ fluticasone propionate,⁹¹ fluticasone furoate,⁹² and mometasone furoate have shown such activity.^{93,94} The impact of intranasal steroids on ocular symptoms is not without a possible adverse effect; a preliminary study evaluating IOP showed a significant reduction in IOP with intranasal steroid discontinuation in patients with preexisting evidence of increased IOP.⁹⁵

Cyclosporine

Although cyclosporine has been available for >20 years in various areas of organ transplantation, its lipophilicity presented a unique challenge to generate a

solution or suspension to be delivered to the ocular surface.⁹⁶ Topical 2% cyclosporine A in preservative-free artificial tears showed improved signs and symptoms of patients with severe vernal keratoconjunctivitis and had no observed side effects over the 14-week course of the study.⁹⁷ Cyclosporine A, an immunosuppressant, has the potential to increase tear fluid secretion and has been approved for the treatment of dry eye syndromes. Topical application of 0.1% cyclosporine A eyedrops for 3 days significantly increased lacrimation. This response was completely blocked by preexposure to 1% capsaicin.⁹⁸

Immunotherapy

The efficacy of allergen immunotherapy is well established, although it appears that AR responds better to treatment than allergic conjunctivitis. Although initial studies of allergen immunotherapy did not specifically address ocular symptoms in a separate manner,⁹⁹ more recent clinical studies have started to identify improvement in ocular signs and symptoms in a separate category.^{100–102} This includes the standard use of subcutaneous immunotherapy¹⁰³ and the investigational forms of sublingual immunotherapy.^{104–106} In a more recent study, the clinical effect on rhinitis and conjunctivitis achieved during specific subcutaneous immunotherapy even persisted for years after termination of treatment (5-year follow-up). The visual analog scale reflected a two- to threefold improvement for both ocular ($p < 0.001$) and nasal scores ($p < 0.01$) and the conjunctival sensitivity as measured by provocation tests were significantly reduced by >2 logs of allergen from years 2–5 ($p < 0.001$).¹⁰⁷ An evolving treatment for allergies and asthma is sublingual immunotherapy, which was shown in a study to have im-

provement in asthma symptom scores (41% versus placebo group), reduction in nasal symptoms (25% versus placebo group), and the use of rescue medications (10% versus placebo group), but having no effect on ocular symptoms.¹⁰⁸ In an earlier study, grass pollen seasonal rhinitis was included in this double-blind, randomized, placebo-controlled trial, where throughout the grass pollen season, patients in the active treatment group had significantly lower ($p < 0.05$) total conjunctivitis and ocular redness scores¹⁰⁹ and a more recent study showed a decrease from 32 to 36% in ocular (itchiness and grittiness) symptoms of allergic conjunctivitis.¹¹⁰

Novel Treatment in Development

SEGRAs seem to represent a useful novel therapeutic modality that may complement existing therapeutic principles for the topical and, especially, the systemic treatment of inflammatory diseases. These “dissociated” agents show a separation between anti-inflammatory and immunosuppressive effects and certain side effects of the steroids and thus represent a new class of agents alike to the leukotriene inhibitors and agonists because they do not have the adverse effects profile of steroids but have many of its antiinflammatory effects.¹¹¹ In a model of dry eye disease, induced by atropine sulfate administration and treated with saline, a SEGRA compound had comparable results with dexamethasone while exhibiting an improved side effect profile in IOP and muscle wasting.¹¹² Other preliminary studies showed that the SEGRA compound had less potential for skin atrophy.¹¹³

CONCLUSION

The pharmacologic treatment of allergic conjunctivitis has evolved and consists of agents designed to block various pathways in the IgE mast cell-mediated inflammatory cascade. Oral and topical antihistamines target histamine receptors, preventing histamine-mediated symptoms of allergic conjunctivitis, such as itching, watery eyes, chemosis, and periorbital swelling. Antihistamines may have a minimal effect other inflammatory mediators, but also have a tendency to induce ocular drying, which may limit their use. Although topical mast cell stabilizers block the release of histamine, prostaglandins, and leukotrienes by stabilizing mast cell membranes, they are more useful as prophylaxis because they have no effect on already synthesized inflammatory mediators. Topical multiple-action agents with mast cell-stabilizing activity have more diverse inhibitory effects on the inflammatory cascade and will inhibit preexisting inflammatory mediators and block the synthesis of more inflammatory mediators and thus have a treatment and prophylactic impact on allergic conjunctivitis. Because of their

Table 1 The spectrum of multiple action agents that are available

	Azelastine Optivar	Epinastine Elestat	Ketotifen Zaditor	Olopatadine Patanol	Olopatadine Pataday	Bepotastine Bepreve	Alcaftadine Lastacraft
Rx	Itch	Itch	Itch	Itch	Itch	Itch	Itch
Signs and symptoms							
Dose	1 gtt o.u. b.i.d.	1 gtt o.u. b.i.d.	1 gtt o.u. 8–12 hr	1 gtt o.u. 6–8 hr	1 gtt o.u. q.d.	1 gtt o.u. b.i.d.	1 gtt o.u. q.d.
AEs	Transient stinging, headache, bitter taste (<1% d/c due to AEs)	Burning, infection [URI/cold symptoms] (10%)	Headache and conjunctival injection	Transient stinging/burn (<5%), headache (7%)	Transient stinging/burn (<5%), headache (7%) flu-like symptoms (10%)	Taste perversion <25%, eye irritation, headache, and nasopharyngitis <5%	Transient stinging/burn, headache, and flu-like symptoms (< 4%)
Category	C	C	C	C	C	C	B

Ketotifen is now available over the counter as various formulations (Alaway, Claritin Eye, Zyrtec Itchy Eye, Refresh Eye Itch Relief, and Visine All Day Eye Itch Relief) that is commonly used before initiation of any prescription allergy eye medication.

AEs = adverse events; gtt = drop; o.u. = both eyes; URI = upper respiratory infection.

ability to block the generation of most inflammatory mediators through inhibition of mast cell phospholipase A2, topical corticosteroids represent the most effective treatment approach to persistent and chronic forms of allergic conjunctivitis. However, corticosteroids are less likely to be prescribed because of their increased risk of cataract formation and elevated IOP and the restriction to short-term use. According to current treatment recommendations, allergic conjunctivitis is managed in a stepwise approach (see Fig. 1). Lubricants are initially recommended for disease prevention. In patients who do not respond, pharmacotherapy is prescribed in the following sequence until acceptable relief of symptoms is achieved: topical antihistamines, alone or in combination with nonsteroidal anti-inflammatory drugs; topical antihistamines combined with vasoconstrictors; and multiple action agents with a short course of corticosteroids. Cyclosporine should be considered in those patients who also have a component of a dry eye syndrome (Table 1).

Special points for consideration include the following:

Decongestant ophthalmic solutions should not be used if they become discolored or cloudy.

Intranasal steroids only have a mild effect on ocular symptoms of allergic conjunctivitis (more on seasonal/intermittent than perennial/persistent forms).

All topical antihistamines/multiple-action agents are category C except for alcaftadine.

Oral antihistamines may exacerbate dry eye syndromes and switching to topical agents for the control of ocular allergy symptoms should be considered.

Allergic conjunctivitis commonly involves physiological features of dry eye syndrome.

Topical multiple-action agents will inhibit preexisting inflammatory mediators (*i.e.*, histamine) and block the synthesis of more inflammatory mediators that accentuate the late-phase response, thus having a treatment and prophylactic impact on allergic conjunctivitis.

Ocular steroids can be used in severe cases as a “burst” when there are no signs of viral infection.

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