Ophthalmics for Allergic Conjunctivitis Review

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FDA-Approved Indications

Drug	Manufacturer	Approved age range	Indication(s)
Ophthalmic Antihistamines			
alcaftadine (Lastacaft™)[1]	Allergan	≥ 2 years	Prevention of itching of the eye due to allergic conjunctivitis
azelastine (Optivar®)[2]	generic, Meda	≥ 3 years	Treatment of itching of the eye associated with allergic conjunctivitis
bepotastine (Bepreve™)[3]	ISTA	≥ 2 years	Treatment of ocular itching associated with allergic conjunctivitis
emedastine (Emadine®)[4]	Alcon	≥ 3 years	Temporary relief of the signs and symptoms of allergic conjunctivitis
epinastine (Elestat™)[5]	Allergan	≥ 3 years	Prevention of itching of the eye due to allergic conjunctivitis
ketotifen (Alaway™OTC, Zaditor® OTC, Zyrtec® Itchy Eye OTC)[6]	generic	≥ 3 years	Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander
olopatadine (Patanol®)[7]	Alcon	≥ 3 years	Treatment of the signs and symptoms of allergic conjunctivitis
olopatadine (Pataday™)[8]	Alcon	≥ 3 years	Treatment of ocular itching associated with allergic conjunctivitis
Ophthalmic Mast Cell Stabilizers			
cromolyn (Crolom®)[9]	generic	≥ 4 years	Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
lodoxamide (Alomide®)[10]	Alcon	≥ 2 years	Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis
nedocromil (Alocril®)[11]	Allergan	≥ 3 years	Treatment of itching associated with allergic conjunctivitis
pemirolast (Alamast®)[12]	Vistakon	≥ 3 years	Prevention of itching of the eye due to allergic conjunctivitis
Others			
ketorolac (Acular®)[13]	generic	≥ 3 years	Temporary relief of ocular itching due to seasonal allergic conjunctivitis Treatment of post-operative inflammation in patients who have undergone cataract extraction
loteprednol (Alrex®)[14]	Bausch & Lomb	≥ 12 years	Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis

Overview

Conjunctivitis, or inflammation of the conjunctiva, may occur secondary to infectious or non-infectious stimuli. Seasonal and perennial allergic conjunctivitis are non-infectious types of

conjunctivitis and are among the most common ophthalmic problems. Estimated prevalence of seasonal allergic conjunctivitis is 15 percent, and the condition occurs in both adults and children.[15] Signs and symptoms of the disorder may cause extreme discomfort. Seasonal allergic conjunctivitis usually presents bilaterally and occurs during seasonal exposure to allergens such as ragweed. Perennial allergic conjunctivitis has a similar initial presentation; however, symptoms do not have seasonal variation. The range of symptoms varies from itching and redness to swelling, excessive lacrimation, and mucous discharge. As with allergic rhinitis, avoidance of identified allergens is a part of comprehensive therapy for allergic conjunctivitis.

The American Academy of Ophthalmology recommends a step-wise approach to the patient with allergic conjunctivitis in their 2008 treatment guidelines.[16] The guidelines do not recommend any particular ophthalmic antihistamine; any of the ophthalmic antihistamines may be used as therapy for allergic conjunctivitis. For persistent or frequent symptoms, an agent with mast cell stabilizer activity may be used. Short courses of ophthalmic corticosteroids may be used to treat disease flares or severe symptoms.

Pharmacology

Therapeutic efficacy is independent of pharmacological activity.[17]

Drug	Antihistamine	Anti-Inflammatory	Mast Cell Stabilizer
Ophthalmic Antihistamines			
alcaftadine (Lastacaft)[18]	X		X
azelastine (Optivar)[19]	X		X
bepotastine (Bepreve)[20]	X		X
emedastine (Emadine)[21]	X		
epinastine (Elestat)[22]	X		X
ketotifen[23]	X		X
olopatadine (Patanol)[24]	X		X
olopatadine (Pataday)[25]	X		X
Ophthalmic Mast Cell Stabilizers			
cromolyn (Crolom)[26]			X
lodoxamide (Alomide)[27]			X
nedocromil (Alocril)[28]			X
pemirolast (Alamast)[29]			X
Others			
ketorolac (Acular)[30]		X	
loteprednol (Alrex)[31]		X	

Pharmacokinetics

Drug	Systemic absorption	Preservative
Ophthalmic Antihistamines		
alcaftadine (Lastacaft)[32]	Below level of detection	benzalkonium chloride
azelastine (Optivar)[33]	Systemic absorption does occur with reported plasma concentrations of 0.02 to 0.25 ng/mL after 56 days of treatment	benzalkonium chloride
bepotastine (Bepreve)[34]	Plasma concentrations peak at 1 to 2 hours post-instillation, with a maximum concentration of 7.3 ng/mL.	benzalkonium chloride
emedastine (Emadine)[35]	Below level of detection	benzalkonium chloride
epinastine (Elestat)[36]	Average maximum plasma concentrations of 0.04 ± 0.014 ng/ml were reached after about two hours	benzalkonium chloride
ketotifen[37]	Below level of detection	benzalkonium chloride
olopatadine (Patanol)[38]	Measurable levels within two hours of dosing ranged from 0.5 to 1.3 ng/mL in a small percentage of patients	benzalkonium chloride
olopatadine (Pataday)[39]	no data	benzalkonium chloride
Ophthalmic Mast Cell Stabilizers		
cromolyn (Crolom)[40]	Systemic absorption has been reported, but at low levels	benzalkonium chloride
lodoxamide (Alomide)[41]	Below level of detection	benzalkonium chloride
nedocromil (Alocril)[42]	Less than four percent of the total dose is systemically absorbed.	benzalkonium chloride
pemirolast (Alamast)[43]	The mean peak plasma concentration was low (4.7 ng/mL) occurring at about 0.5 hours following topical administration	lauralkonium chloride
Others		
ketorolac (Acular)[44]	Approximately 20 percent of patients had detectable systemic amounts of ketorolac after 10 days of ocular topical therapy	benzalkonium chloride
loteprednol (Alrex)[45]	below level of detection	benzalkonium chloride

Contraindications/Warnings[46,47,48,49,50,51,52,53,54,55,56,57,58]

Loteprednol (Alrex) is contraindicated in patients with most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.[59]

For all agents in the class, if a patient has a hypersensitivity to a product or its excipients, the patient should not receive the product.

The agents in this review should not be used to treat contact lens-related irritation. All agents contain the preservative benzalkonium chloride which may be absorbed by soft contact lenses, therefore should not be instilled while wearing contact lenses. Lenses may be reinserted after 10 minutes following administration.

Drug Interactions

Due to the topical route of administration of the products, clinically significant systemic drug interactions are not well identified*.*

Ketorolac (Acular) has been safely given with ophthalmic antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.[60]

Adverse Effects

Drug	Stinging/ Burning	Headache	Eyelid edema	Rash	Rhinitis	Conjunctival injection	Blurred vision
Ophthalmic Antihistamines							
alcaftadine (Lastacaft)[61]	<4	<3	nr	nr	nr	nr	nr
azelastine (Optivar)[62]	30	15	nr	nr	1-10	nr	1-10
bepotastine (Bepreve)[63]	2-5	2-5	nr	nr	nr	nr	nr
emedastine (Emadine)[64]	<5	11	nr	nr	<5	nr	<5
epinastine (Elestat)[65]	1-10	1-3	nr	nr	1-3	nr	nr
ketotifen[66]	<5	10-25	<5	<5	10-25	10-25	nr
olopatadine (Patanol)[67]	<5	7	<5	nr	<5	nr	<5
olopatadine (Pataday)[68]	<5	<5	<5	nr	<5	nr	<5
Ophthalmic Mast Cell Stabilizers							
cromolyn (Crolom)[69]	reported	nr	reported	nr	nr	reported	reported
lodoxamide (Alomide)[70]	15	1.5	<1	<1	nr	nr	1-5
nedocromil (Alocril)[71]	10-30	40	nr	nr	1-10	nr	nr
pemirolast (Alamast)[72]	<5	10-25	nr	nr	10-25	nr	nr
Others							
ketorolac (Acular)[73]	up to 40	reported	nr	nr	nr	nr	reported
loteprednol (Alrex)[74]	5-15	<15	nr	nr	<15	5-15	5-15

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Bepotastine (Bepreve) has been noted to cause a mild taste following instillation in approximately 25 percent of subjects.[75]

Special Populations[76,77,78,79,80,81,82,83,84,85,86,87,88]

Pediatrics

Most of the agents in this class are safe and effective in children as young as three years of age. Cromolyn sodium (Crolom), four years or older, and loteprednol (Alrex), 12 years and older, are exceptions. Alcaftadine (Lastacaft), lodoxamide (Alomide), and bepotastine (Bepreve) are approved for use in children as young as two years old.

ketotifen (Zaditor) in children

Efficacy and safety of ketotifen 0.025% were evaluated in a double-blind, multicenter, placebo-controlled trial.[89] The study was of conjunctival allergen challenge (CAC) design using both single and multiple doses. Patients (n=133) were between eight to 16 years old and exhibited a positive response to allergen challenge. Patients were given one drop of ketotifen in one eye and placebo in the other eye. CAC was administered 15 minutes and eight hours after the dose. Patients with a positive allergen reaction in both eyes were randomized to multiple dose treatment (n=60). Patients administered ketotifen in one eye and placebo in the other eye twice daily for four weeks. CAC was performed eight hours after the last dose. Of the 55 evaluable patients, ketotifen significantly reduced ocular itching compared to placebo after CAC ($p<0.001$). Hyperemia, chemosis, and lid swelling were also significantly reduced with ketotifen ($p=0.031$). Adverse effects were similar to placebo.

olopatadine 0.2% (Pataday) in children

Olopatadine 0.2% was evaluated for safety in 126 children and adolescents (ages three to 17 years) with asymptomatic eyes in a six-week, randomized, double-blind trial.[90] Patients were randomized to once daily olopatadine 0.2% or vehicle. Safety was assessed at three visits and three interviews. No clinically relevant treatment-related changes in visual acuity, intraocular pressure, slit-lamp assessments, fundus examinations, or cardiovascular parameters were observed. Adverse events were mild or moderate.

Pregnancy

Alcaftadine (Lastacaft), cromolyn, emedastine (Emadine), lodoxamide, and nedocromil (Alocril) are Pregnancy Category B; all the other ophthalmic products in this review are classified as Pregnancy Category C.

Dosages

Drug	Dosage (in affected eye(s))	Availability
Ophthalmic Antihistamines		
alcaftadine (Lastacaft)[91]	One drop once daily	0.25% solution (3mL)
azelastine (Optivar)[92]	One drop twice daily	0.05% solution (6 mL)
bepotastine (Bepreve)[93]	One drop twice daily	1.5% solution (10 mL)
emedastine (Emadine)[94]	One drop up to four times daily	0.05% solution (5 mL)
epinastine (Elestat)[95]	One drop twice daily	0.05% solution (5 mL)
ketotifen[96]	One drop twice daily every eight to 12 hours	0.025% solution (Zaditor/OTC: 5 mL; Alaway OTC: 10 mL; Zyrtec Itchy Eyes: 5 mL)
olopatadine (Patanol)[97]	One drop twice daily at an interval of six to eight hours	0.1% solution (5 mL)
olopatadine (Pataday)[98]	One drop once daily	0.2% solution (2.5 mL)
Ophthalmic Mast Cell Stabilizers		
cromolyn (Crolom)[99]	One to two drops four to six times daily	4% solution (10 mL)
lodoxamide (Alomide)[100]	One to two drops four times daily for up to three months	0.1% solution (10 mL)
nedocromil (Alocril)[101]	One to two drops twice a day	2% solution (5 mL)
pemirolast (Alamast)[102]	One to two drops four times daily	0.1% solution (10 mL)
Others		
ketorolac (Acular)[103]	One drop four times a day For cataracts: One drop four times daily beginning 24 hours after surgery and continuing through the first two weeks of the postoperative period	0.5% solution (3, 5, 10 mL)
loteprednol (Alrex)[104]	One drop four times daily (shake well)	0.2% suspension (5, 10 mL)

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information submitted by manufacturers. Search strategy included the FDA-approved use of all drugs in this class and allergic conjunctivitis. Randomized, controlled, comparative trials with multiple doses for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and clinical importance.

Many of the studies of the ophthalmic agents for the treatment of allergic conjunctivitis are performed as single-dose studies. The studies give very little information regarding efficacy and safety in chronic use of these agents. Additionally, many of the studies are done using the conjunctival allergen challenge (CAC) model in an effort to induce an allergic response and evaluate drug efficacy in a short-term model. The number of patients enrolled in the studies was generally less than 100. Several comparisons to levocabastine appear in the literature; levocabastine is no longer available in the United States.

Allergic Conjunctivitis

alcaftadine (Lastacaft)

Fifty-eight subjects with a history of allergic conjunctivitis were enrolled in a double-masked, multicenter, vehicle-controlled study.[105] Outcome measures were ocular itching and conjunctival redness. The signs and symptoms of allergic conjunctivitis were induced in the subjects by a conjunctival allergen challenge (CAC). The subjects were randomized to be given either one drop of alcaftadine 0.25% ophthalmic solution bilaterally or vehicle bilaterally. Alcaftadine significantly lessened conjunctival redness after both 15 minutes and 16 hours of the drug administration. With an onset of action within three minutes and the duration of action lasting up to 16 hours, alcaftadine was more effective than its vehicle in preventing ocular itching.

azelastine (Optivar), epinastine (Elestat), and ketotifen (Zaditor)

A study compared the short-term (five-minute) ocular comfort and drying effects of epinastine, azelastine, and ketotifen in 40 patients with allergic conjunctivitis. This was a single-center, randomized, double-blind, crossover study.[106] At the first visit, patients were randomized to receive one drop of epinastine in one eye and either azelastine or ketotifen in the other eye. Ocular comfort was assessed by patients on an 11-point scale immediately and at 0.5, one, two, and five minutes after instillation. Patients were also asked to describe how their eyes felt at three minutes using a standardized list of positive, neutral, and negative descriptor words. The mean comfort score indicated more comfort with epinastine compared with azelastine at 0.5, one, two, and five minutes ($p<0.001$, $p<0.001$, $p=0.001$, and $p=0.019$) and compared with

ketotifen immediately after instillation (p=0.014). The mean ocular comfort score was significantly lower with ketotifen compared with azelastine at 0.5, one, and two minutes (p=0.001, p=0.023, and p=0.028). A majority (85 percent) of patients chose positive comfort descriptors to describe epinastine versus 34 percent with azelastine.

bepotastine (Bepreve)

A randomized, double-masked, placebo-controlled, multicenter CAC study compared 130 patients with allergic conjunctivitis with bepotastine 1%,1.5%, and placebo.[107] Both strengths of bepotastine significantly reduced CAC ocular itching at onset of action and at least for eight hours after dosing (p≤0.0001). Conjunctival hyperemia reductions for bepotastine were seen only at onset of action of CAC test (p≤0.0125). Only the 1.5% strength is FDA-approved.

emedastine (Emadine) and ketorolac (Acular)

Thirty-six subjects were randomized into two groups in a double-blind, single-center crossover study comparing emedastine 0.05% and ketorolac 0.5%.[108] The first group received emedastine 0.05% in one eye and placebo in the other eye. The second group received ketorolac 0.5% in one eye and placebo in the other eye. Ten minutes after instillation, patients underwent allergen challenge. After the challenge, patients graded ocular itching and were assessed for hyperemia. Approximately 14 days later, subjects entered the crossover treatment phase. Emadastine 0.05% significantly inhibited ocular itching and redness (p<0.05). Ketorolac 0.5% failed to significantly inhibit ocular itching or redness. Patients also stated emedastine was more comfortable than ketorolac upon administration (p<0.05).

emedastine (Emadine) and ketotifen (Zaditor)

Forty-five subjects were enrolled in a single-center, double-masked study to compare efficacy of two agents and placebo for temporary relief of ocular itching related to allergic conjunctivitis.[109] Patients were randomized to treatment in one of three groups: emedastine 0.05% in one eye and placebo in the other; ketotifen 0.025% in one eye and placebo in the other; or emedastine 0.05% in one eye and ketotifen 0.025% in the other. Patients eliciting a positive allergic response were identified. In 25 subjects, bilateral CAC was performed five minutes after study medication instillation. In a second group of 20 subjects, CAC was performed 15 minutes after medication instillation. Both emedastine and ketotifen significantly inhibited itching (p<0.05) compared with placebo at all time points after the five- and 15-minute CAC. Itching scores were similar in the two active treatment groups. No adverse events were reported.

epinastine (Elestat) and olopatadine (Patanol)

Olopatadine 0.1% and epinastine 0.05% were compared for safety and itching and conjunctival redness prevention using the CAC model in a prospective, randomized, double-blind study.[110] Screening for response to allergen challenge (n=96) occurred prior to randomization. A total of 66 evaluable patients with allergic conjunctivitis were randomized to olopatadine in one eye with epinastine in the other eye, olopatadine in one eye with placebo in the other, or epinastine in one eye with placebo in the other eye. Allergen was applied to both eyes five minutes after treatment administration. Olopatadine was associated with significantly less itching and conjunctival redness than contralateral epinastine-treated eyes (p=0.003, p<0.001, respectively). Olopatadine-treated eyes also had less chemosis (p<0.001), ciliary redness (p<0.001), and episcleral redness (p<0.001) than epinastine-treated eyes in the single-dose CAC model trial.

ketotifen (Zaditor) and nedocromil (Alocril)

In a double-blind, single-center study of 85 patients, the CAC model was used to test three treatments: ketotifen 0.025%, nedocromil 2%, and placebo.[111] Patients (n=85) underwent CAC screening on two occasions prior to randomization. During two different visits 14 days apart, subjects (n=59) were randomized to one of the three treatment groups. Allergen challenges were conducted at five minutes post-treatment at the first visit and at 12 hours post-treatment at the second visit. Ketotifen-treated eyes exhibited significantly less ocular itching than both nedocromil-treated and placebo-treated eyes at both the five-minute and 12-hour post-treatment challenges ($p<0.05$ for all). Ketotifen was tolerated as well as placebo. Ketotifen instillation was significantly more comfortable than nedocromil up to 10 minutes after instillation ($p<0.05$). Based on comfort and subjective efficacy, 60 percent of patients preferred ketotifen, 21 percent preferred nedocromil, and 19 percent preferred placebo.

ketotifen (Zaditor) and olopatadine (Patanol)

A randomized, double-masked, single-center, CAC study comparing ketotifen 0.025% and olopatadine 0.1% was conducted in 53 patients.[112] Primary efficacy endpoints were ocular itching and subject satisfaction. Itching was graded on a five-point scale at three, five, and ten minutes post-challenge. After screening, the remaining 32 patients were randomized to two groups. The first group instilled olopatadine one drop in the right eye and ketotifen one drop in the left eye. The second group instilled ketotifen one drop in the right eye and olopatadine one drop in the left eye. Twelve hours after instillation, subjects underwent allergen challenge. Efficacy scores for olopatadine were significantly higher than ketotifen at three and five minutes post-challenge ($p<0.05$). Olopatadine-treated eyes were rated significantly more comfortable than those treated with ketotifen both immediately after drug instillation and 12 hours later ($p<0.05$).

In a double-masked study, 66 patients with seasonal allergic conjunctivitis were randomized to treatment with ketotifen 0.025% or olopatadine 0.1% instilled twice daily.[113] Patients were assessed on days five and 21. Responder rate was higher on day five for ketotifen versus olopatadine (72 and 54 percent for patient assessment; 88 and 55 percent for investigator assessment, respectively). Responder rates on day 21 for ketotifen versus olopatadine were 91 percent versus 55 percent for patient assessment and 94 versus 42 percent for investigator assessment, respectively. Severity scores for hyperemia and itching were significantly lower for the ketotifen group. In both groups, the most common adverse effects were burning/stinging and headache. Patients rated both drugs similarly for comfort.

A comparison of olopatadine 0.1% and ketotifen 0.025% on patient preference was performed in 100 patients with allergic conjunctivitis.[114] In the European double-blind study, patients administered olopatadine and ketotifen to a single eye on an as-needed basis up to two drops daily per eye over four weeks. After four weeks, patients' preference was assessed using five questions regarding comfort, preference, and efficacy in reducing signs and symptoms. Olopatadine was preferred by 81 percent of patients based on comfort and efficacy in reducing symptoms, and patients would select olopatadine at their next doctor's visit ($p<0.0001$). Most patients (76 percent) based their preference on efficacy and comfort ($p<0.0001$).

In a randomized, double-blind trial, ketotifen 0.025% and olopatadine 0.1% ophthalmic solutions were compared in patients with seasonal allergic conjunctivitis.[115] Forty-nine patients were randomized to ketotifen, olopatadine, or artificial tears administered two drops twice daily to both eyes for 30 days. Thirty-nine patients completed the trial. At baseline, day 15, and the end of

the trial, clinical sign and symptom scores for itching, tearing, physician's assessment of eyelid swelling, redness and chemosis, conjunctival cytology specimens, and reports of adverse events were reported. For clinical sign and symptom scores, both active treatment groups reported significant improvement in tearing and itching at day 15 and 30 compared to baseline. The artificial tears group experienced a significant reduction in tearing at both days 15 and 30. Inflammatory markers were significantly lower in active treatment groups at both day 15 and 30 compared to artificial tears. Adverse events were not reported during the one-month trial.

loteprednol etabonate (Alrex) and olopatadine (Patanol)

In a single-center, double-masked CAC study, 50 subjects were randomized to receive olopatadine 0.1%, loteprednol 0.2%, or placebo.[116] One drop was instilled in each eye. Because loteprednol requires a higher dose loading period for efficacy, patients in the loteprednol group received loteprednol bilaterally four times daily for 14 days. Fifteen minutes after drug instillation, patients underwent allergen challenge. Subjects evaluated itching at three, five, and ten minutes after challenge using a standardized five-point scale. The investigator evaluated redness at 10, 15, and 20 minutes after challenge. Difference in inhibition of itching and redness was clinically significant ($\geq$ one unit difference) and statistically significant ($p<0.05$) in favor of olopatadine compared with loteprednol at all three time points.

olopatadine (Patanol) and azelastine (Optivar)

In a prospective, multicenter, double-masked, allergen challenge study, 180 patients were randomized to one of three treatment groups: olopatadine 0.1% solution in one eye and azelastine 0.05% solution in the other eye; olopatadine in one eye and placebo in the other eye; or azelastine in one eye and placebo in the other eye.[117] The placebo was artificial tears. Two screening phases were performed to identify appropriate allergen challenge. Five minutes after the drops were instilled, subjects (n=111) were bilaterally challenged with an allergen concentration previously determined to elicit a positive conjunctival allergic response. Subjects rated itching every 30 seconds for a total of 20 minutes. Both treatments were significantly more effective than placebo at reducing itching post-challenge. Olopatadine was significantly more effective than azelastine in reducing itching at 3.5 minutes through 20 minutes post-challenge (average mean unit difference of -0.31; $p<0.05$) in the CAC model. Single-dose administration did not result in any serious adverse events.

olopatadine (Patanol) and ketorolac (Acular)

Olopatadine 0.1% solution and ketorolac 0.5% solution were compared in a randomized, double-blind, cross-over study.[118] Patients received active treatment in one eye (either olopatadine or ketorolac) and placebo in the other eye. Allergen challenge was administered 27 minutes after drug instillation. Two weeks later, active drug was applied to the other eye. Olopatadine was significantly more effective than ketorolac ($p<0.001$) and placebo ($p<0.0001$) in reducing hyperemia and ocular itching at all time points (three, ten, and 20 minutes). Ketorolac was not associated with a reduction in itching. Olopatadine was also significantly more comfortable than ketorolac as reported by subjects immediately following drug instillation ($p<0.05$).

olopatadine (Pataday) and olopatadine (Patanol)

In a double-blind, 24-hour study, efficacy of two doses of olopatadine 0.1% was compared to one dose of olopatadine 0.2% in prevention of ocular itching associated with allergic conjunctivitis.[119] Using conjunctival allergen challenge (CAC), no significant difference in the mean itching scores between two drops of olopatadine 0.1% and one drop of olopatadine 0.2% was observed. Both products showed significant activity at the 24-hour time point and were statistically superior to placebo. No adverse events occurred were reported.

pemirolast (Alamast) and nedocromil (Alocril)

Pemirolast 0.1% and nedocromil 2% were compared in 80 patients with seasonal allergic conjunctivitis over eight weeks in a double-blind, randomized, active-control trial.[120] Both agents were applied twice daily for eight weeks, although pemirolast is indicated for four times daily dosing. At each visit during the eight-week study, patients rated pemirolast instillation as more comfortable. At the study's end, 58 percent of patients reported no signs or symptoms of allergic conjunctivitis at work or school with pemirolast compared to 28 percent with nedocromil (p=0.005). No significant differences in signs or symptoms of seasonal allergic conjunctivitis (redness, chemosis, itching, eyelid swelling) were found between pemirolast and nedocromil. Adverse events were similar in both groups.

Cataract Surgery

ketorolac (Acular) and diclofenac (Voltaren®)

In a double-blind trial, 30 patients were randomized to receive ophthalmic irrigation solution and diclofenac or ophthalmic irrigation solution and ketorolac.[121] At seven and 15 minutes after eyedrop application, corneal sensory thresholds were measured. No significant decrease in corneal sensory thresholds was found with diclofenac or ketorolac compared with control at baseline (p=0.50), seven minutes (p=0.41), or 15 minutes (p=0.82). There was a small, but not statistically significant (p=0.28), trend of more burning with ketorolac than diclofenac. In a similar study by the same principal investigator, patients treated with ketorolac and diclofenac reported similar rates of pain relief and stinging on instillation associated with refractive surgery.[122]

ketorolac (Acular) and prednisolone acetate

In a double-blind trial, 59 patients requiring cataract extraction were randomized to receive either ketorolac 0.5% or prednisolone acetate 1%. The drugs were administered on the following schedule: one to two drops four times daily for the first week; three times daily for the second week; two times daily for the third week; and once daily for the fourth week.[123] At day 28, both treatments produced comparable reductions in intraocular inflammation and pain after cataract surgery and were well tolerated by patients. No adverse events were reported.

ketorolac (Acular) and rimexolone (Vexol®)

Starting the day after cataract extraction, 36 patients were randomized to receive either ketorolac 0.5% or rimexolone 1% in a randomized, double-blind trial.[124] Each agent was used four times per day. No statistically significant difference in any measurement of postoperative inflammation between the two groups was observed.

Summary

Numerous comparative trials using allergic conjunctivitis agents have been conducted. The trials used one-time administration of a single dose in the eye and evaluated effects based on a CAC model. From the results of the trials, it is difficult to declare one agent superior to another. Another factor used to evaluate the drugs is ocular comfort. This evaluation was also made from one-time single dose trials. Again, the results of the trials do not support superiority of any product in the class.

Azelastine (Optivar), bepotastine (Bepreve), epinastine (Elestat), ketotifen (Zaditor), nedocromil (Alocril), and olopatadine 0.1% (Patanol) require administration two or three times daily versus other products which require four times per day dosing. Alcaftadine (Lastacaft) and olopatadine (Pataday) 0.2% are administered once daily.

Additionally, ketorolac (Acular) is indicated for reducing inflammation and pain after cataract extraction. Ketorolac 0.5% was compared to other nonsteroidal anti-inflammatory agents and corticosteroid preparations. Efficacy and tolerability were comparable in the clinical trials.

References

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