It is time to take stock of conditions that affect 25 percent of your patients: seasonal and panseasonal allergic conjunctivitis. While from one point of view, ocular allergy research and new treatments certainly know how to ride the coattails of research in other forms and sites of inflammation, interest in ocular allergy also stems from the fact that the ideal drug has not yet come to hand. In this article, we’ll provide news about the more pragmatic clinical science of ocular allergy.

Our Methods

This article is the result of a comprehensive literature search of clinical studies from 2013 to 2015, combined with information from studies listed on clinicaltrials.gov whose results have yet to be published. Much of what has been reported has actually focused on chronic allergy with a proliferative component. While diseases such as vernal and allergic keratoconjunctivitis afflict a small percentage of allergy sufferers, the permanent damage to vision that can result from corneal involvement, sometimes in pediatric patients, lends weight to this discussion and warrants a complete investigation into the more disease-modifying treatment options. This year, our mainstays for symptomatic therapy are also being challenged, and the results of new head-to-head comparisons may surprise.

Severe Allergy

Several agents for severe cases of allergy have been the subjects of research this year.

• Cyclosporine. Cyclosporine has won a lot of press this year in allergy. Four peer-reviewed articles highlighted the efficacy of this immunomodulator in ocular allergic disease. While ophthalmologists overseas have treated severe ocular allergy with ad hoc formulations of cyclosporine for years, the results highlighted below, taken with the now-known safety of commercially available Restasis, may make revisiting this immunomodulator worthwhile, particularly in light of its steroid-sparing effect. In a Hong Kong study, researchers analyzed the efficacy of a three-month course of Restasis in 14 pediatric allergic conjunctivitis patients. Eleven were able to taper off steroid treatment after three months, and scores dropped for signs and symptoms ($p<0.0001$).1 A review of VKC treated with cyclosporine and tacrolimus recently summarized the interest in these treatment options, particularly tacrolimus.2 A clinical trial

Researchers are exploring disease-modifying treatment options and not just symptomatic relief.
of a four-week course of 0.05% cyclosporine in 62 VKC patients came out of Turkey this year, and both sign and symptom scores were significantly improved \( (p<0.0001) \).\(^3\)

Also from Hong Kong was a meta-analysis of trials involving cyclosporine use for allergic conjunctivitis (and not VKC or AKC). Investigators identified seven qualifying studies, with 153 patients treated for at least two weeks. Topical cyclosporine was associated with lower composite scores in signs and symptoms compared to placebo, with a pooled standardized mean difference of -1.21. Two of the three studies also found a significant reduction in steroid dependency.\(^4\)

- Tacrolimus. Another large-scale clinical trial investigated the efficacy of twice-daily 0.1% tacrolimus in 1,436 subjects with refractory allergic conjunctivitis with proliferative lesions and/or corneal involvement. At last observation, mean total sign (-9.4) and symptom (-6.3) changes were significant (both, \( p<0.001 \)). A subpopulation of patients who were unresponsive to a previous treatment with cyclosporine \((n=239)\) also showed significant improvement in signs and symptoms, including giant papillae and/or epithelial defects. A significant steroid-sparing effect was observed, with 53.4 percent successfully weaned off steroids after six months of tacrolimus treatment.\(^5\)

Another recent trial of tacrolimus demonstrated that addition of olopatadine to the therapy regimen added no more efficacy than tear substitutes for symptom control.\(^6\) In atopic blepharo-conjunctivitis (ABC), a disease of similar mechanism to atopic dermatitis, tacrolimus was shown to be superior to an immunomodulating newcomer, pimecrolimus, in 338 patients.\(^7\)

Closing the discussion of the more serious allergic diseases were some interesting case reports using subcutaneous omalizumab,\(^8\) or supratarsal injections of triamcinolone\(^9\) for successful treatment of recalcitrant VKC.

Another interesting case report touched on the use of rebamipide, recently approved in Japan for dry eye, in patients with both dry eye and refractory allergic diseases.\(^10\) Results indicated that rebamipide might also be useful for both proliferative and non-proliferative allergic disease. Dry eye/allergy comorbidity is extremely common,\(^11\) and might require creative approaches to treatment. It is not surprising really that dry-eye therapy is effective for allergy and perhaps some allergy therapy is effective for dry eye, when we consider the common threads from which ocular surface inflammation is woven.

### Allergic Interplay

A meta-analysis was performed on clinical trials of allergic ocular disease involving the oral leukotriene antagonist, montelukast. In six comparable trials, oral montelukast improved ocular symptom scores better than placebo, but not better than oral antihistamine.\(^12\) This is notable since we previously compared the effects of oral antihistamines versus topical ophthalmic anti-allergic agents, and found that topical therapy wins every time.\(^13\)

Similarly, several papers were published this year on the eye-nose nexus. Allergic conjunctivitis was shown to have 95-percent comorbidity in patients with allergic rhinitis.\(^14\) The possible anatomical and functional relationships between the eye and nose were reviewed, and a case made for bidirectional flow.\(^15\) Conjunctival and tear inflammatory cells increased after nasal allergen provocation.\(^16\)

As with oral therapy, we’ve investigated the claims that nasal anti-allergic therapy might be effective for ocular allergy.\(^13,17,18\) While this concept is attractive, especially for allergists wanting to simplify therapies, it is unlikely to succeed given the magnitude of ocular anti-allergic response that’s required.

Our literature review also revealed clinical trials of immunotherapy addressing “rhinoconjunctivitis.” However, a closer look revealed that these studies do not address ocular endpoints in a well-controlled fashion. We shall see if more stringent requirements for allergic disease indications will translate in the years to come to better-controlled ocular endpoints in immunotherapy trials. One systematic review of 13 trials and 1,037 subjects concluded that sublingual therapy, not yet available in the United States, was moderately successful in improving conjunctival symptoms.\(^19\)

### Salve for Symptoms

Switching gears, let’s discuss what’s new in symptomatic relief of ocular allergy, particularly for relief of the itching that most of our patients suffer.

The pooled per-protocol results from the two pivotal conjunctival allergen challenge bepotastine trials re-
sponsible for the U.S. approval of this drug were published in 2014. By way of nomenclature, per-protocol populations are those subjects who complete a clinical trial with no major protocol deviations, which is different from the intent-to-treat population, which is composed of all subjects treated, independent of how well the protocol was followed. Thus, the per-protocol population is usually a cleaner assessment of drug efficacy.

In the bepotastine trial, out of 157 subjects, 140 were identified as the per-protocol population. Differences in mean ocular itching scores were statistically significant (p < 0.001) at all visits and time points. The onset and eight-hour duration data were also clinically significant, indicated by a one-unit minimal magnitude of difference from placebo. Differences in itch scores recorded at the 16-hour allergen challenge were highly statistically significant, at 0.8 (three minutes post-challenge), 1.0 (five minutes post-challenge) and 0.9 (seven minutes post-challenge) unit differences from placebo, but these were not considered clinically significant since two of the three time points did not demonstrate a full one-unit change.

Itching was also assessed as the percentage of subjects with complete resolution of itching. This is another useful parameter with which new anti-allergic molecules are assessed. The majority of subjects treated with bepotastine reported zero itching at three minutes post-challenge, the peak time for itching response. This total control was maintained at eight hours for one-third of the treated subjects. Since prevention of itching is the indication for which these antihistamines are approved, studying the itching effect from various perspectives has proven very useful in teasing out the benefits afforded of one antihistamine over another. These itching results were then confirmed in an allergist-based trial in seasonal allergic conjunctivitis.

**International Research**

Epinastine (Elestat, Allergan) is another antihistamine whose efficacy in the CAC was published last year, though it’s been eclipsed in the United States by Allergan’s subsequent release of alcaftadine (Lastacaft), which demonstrates superior efficacy and duration. Nevertheless, alcaftadine is not available as yet in Japan, and epinastine is still actively prescribed and investigated in Asia. In fact, many CAC studies are ongoing in Japan due to the alarming incidence and increasing severity of cedar pollen allergic conjunctivitis, considered a health hazard on a national level.

In the epinastine study, it was compared to placebo and olopatadine 0.1% (Patanol, Alcon), the only concentration available outside of the United States. Results showed epinastine to be superior to placebo for both itching and redness at four hours and eight hours, and non-inferior to olopatadine 0.1% when challenged at four hours after dosing. A subsequent Japanese study overseen by our research firm, Ora, and sponsored by Alcon Japan, assessed olopatadine versus epinastine in a contralateral-eye CAC study. It demonstrated the superiority of olopatadine. This latter study in a Japanese population confirmed the results of an earlier U.S. trial that demonstrated olopatadine to be superior to epinastine. This finding also attests to the consistency of results across populations that can be expected when using the CAC model to assess ocular allergic agents.

Some other comparative studies in anti-allergics were completed outside the United States. Chronic allergic conjunctivitis is always a challenge, and was the subject of two peer-reviewed articles. In China, the efficacy of 1% flurometholone was compared to the NSAID, 0.1% pranoprofen, both used q.i.d. for four weeks in 75 patients. Signs decreased more significantly in flurometholone-treated patients at day seven, after which time reductions tapered off. Flurometholone also did better in symptomatic relief on day three. Interestingly, a better clinical outcome was observed in patients under 30 years of age, perhaps indicating that the disease itself becomes more complex with age, or that with accumulating co-morbidities it’s harder to treat. Due to a slight IOP effect in the flurometholone group, the authors advised initiating combination therapy for three to five days, followed by maintenance therapy with an NSAID alone in patients with chronic allergy.

In Turkey, olopatadine 0.1% combined with flurometholone 0.1% versus olopatadine with ketorolac 0.4% was evaluated in 52 seasonal allergic conjunctivitis patients. The unique study design involved instilling both drops in one eye versus placebo in the contralateral eye. Olopatadine was instilled b.i.d. and the steroid or NSAID q.i.d. for 10 days. Redness, mucus secretion, chemosis and eyelid edema were all statistically superior in the flurometholone-olopatadine group than in the olopatadine-NSAID group.

A French study in 75 subjects compared a preserved formulation of olopatadine to preservative-free ketotifen 0.025% in treating seasonal allergic conjunctivitis. Resolution of signs and symptoms was assessed with b.i.d. treatment for 28 days. The composite score for signs and symptoms improved significantly for ketotifen, and no significant difference was observed between this anti-allergic and olopatadine 0.1%.

**Exploring Alcaftadine**

Alcaftadine (Lastacaft) is the newest chemical entity to be approved for prevention of ocular itching associated with allergic conjunctivitis, and two papers have been published investigating the comparative efficacy of olopatadine 0.2% to alcaftadine 0.25%. These are the only two antihistamines
Table 1. Anti-Allergic Drugs Tested Clinically, 2014 to 2015

<table>
<thead>
<tr>
<th>Drug/Sponsor</th>
<th>Mechanism of Action</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
</table>
| EB-101       | IL-1 antagonist     | Chronic AC | Phase II complete  
| Eleven Biotherapeutics |                  |            | did not meet primary endpoint of itching |
| Dexamethasone-Depo | corticosteroid   | Chronic AC | Phase II underway  
| Ocular Therapeutix |                  |            | punctal plug depot showed positive results |
| Fluorometholone | corticosteroid     | Chronic AC | Study 1: superior to pranoprofen, (n=75)  
| non-sponsored studies |                  |            | Study 2: superior in combination with olopatadine versus ketorolac + olopatadine (n=52) |
| Triamcinolone | steroid, supratarsal | Recalcitrant VKC | two doses, 1 month apart; no additional anti-allergic meds  
| Non-sponsored study |                  |            | cobblestones, erosions completely resolved at 18 months |
| Cyclomolone | immunomodulator     | VKC chronic AC | VKC study (n=62), AC meta-analysis (n=153)  
| Non-sponsored studies | calcineurin inhibitor |            | improvements in signs and symptoms in both reports |
| Tacrolimus | immunomodulator     | refractive AC VKC | refractive AC (n=1436), VKC: ± olopatadine (n=21)  
| Non-sponsored studies | calcineurin inhibitor |            | all treatments showed improvements in signs/symptoms |
| Tacrolimus/Pimecrolimus | immunomodulator | Atopic blepharo-conjunctivitis | Both treatments were effective (n=338) |
| Omalizumab | monoclonal antibody | VKC | marked improvements in signs and symptoms at 8 weeks  
| Non-sponsored study | anti-IgE (systemic) |            | proliferative changes resolved at 18 months |
| Montelukast | leukotriene receptor | SAC | meta-analysis of six trials  
| Non-sponsored study | antagonist (systemic) |            | improvements shown in ocular signs and symptoms |
| SLIT Immunotherapy | grass or ragweed | Rhinitis with AC | FDA approved in 2014  
| Merck; Stallergenes | immunogen |            | reduces ocular signs and symptoms in secondary endpoints |
| Rebamipide | mucogenic | Proliferative AC | Giant papillae were reduced in all cases |
| Otsuka Pharmaceutical |                  |          | |
| Cetirizine | antihistamine       | AC | Clinical trials completed  
| Acxiex Therapeutics |                  |            | NDA filing is expected in 2015 |
| Olopatadine 0.77% | dual-acting agent | AC | drug approved by the FDA for q.d. use February 2015  
| Alcon/Novartis |                  |            | superior effects on itching over 0.2% olopatadine |
| Bepotastine 1.5% | dual-acting agent | AC | b.i.d. dosing confirmed (n=140)  
| Bausch & Lomb |                  |            | percentage with minimal or no itching was greater than placebo |
| Epinastine 0.05 % | dual-acting agent | AC | non-inferior to olopatadine at four hours (n=87) |
| Santen Pharmaceutical |                  |          | |
| Olopatadine 0.1% | dual-acting agent | AC | superior to epinastine’s onset of action (n=50) |
| Alcon Japan |                  |          | |
| Olopatadine 0.2% | dual-acting agent | AC | Study 1: non-inferior to preservative-free ketotifen (n=75)  
| Alcon/Novartis |                  |            | Study 2: ongoing trial in China compared to olopatadine 0.1% (n=250) |
| Alcaftadine 0.25% | dual-acting agent | AC | pooled analysis (n=284)  
| Allergan |                  |            | superior to olopatadine 0.2% for itching and for percentage of subjects with minimal or no itching |
available with once-daily dosing, so this comparison was appropriate and necessary for us to understand if there are any benefits offered by treating with the newer compound. While olopatadine is recognized as a dual-acting mast cell stabilizer and antihistamine, the mechanism of alcaftadine appears to be predominantly potent antagonism of H1, H2 and H4 receptors, with receptor affinities that are 10 times higher than that of olopatadine for H1 and H2 receptors. Further, olopatadine has no affinity for the H4 receptor. It’s unknown if alcaftadine’s receptor antagonism is responsible for its known eosinophil chemotactic inhibition and tightening of conjunctival epithelial tight junctions that have been shown preclinically. 

The earlier paper presented the results of one CAC trial in which alcaftadine went head-to-head with olopatadine 0.2% in 127 subjects. Onset and duration of action at 16 and 24 hours after dosing were established. For the primary measure of ocular itching, both actives were statistically significantly superior to placebo at all time points post-CAC for both the 16- and 24-hour duration assessments (p<0.0001). This confirms that both olopatadine 0.2% and alcaftadine 0.25% are effective for symptomatic prevention of itching, all day for up to 24 hours, which is already a feat when we consider how far we’ve come in making our patients more comfortable. However, at three minutes after challenge, the peak time post-CAC for itching because histamine has exploded from mast cells, alcaftadine treatment resulted in significantly lower mean itching scores at the 16-hour duration assessment (p=0.026).

The second alcaftadine versus olopatadine paper, published last year, was on a pooled analysis of two CAC studies (n=284) performed identically to the one described above. In it, patients rated their itch numerically, with 0 signifying no itch and 1 meaning serious itching. Again, at 16 hours after instillation, alcaftadine was superior to olopatadine 0.2% for the first explosive itching that occurs three-minutes after allergen challenge (0.50 vs. 0.87, respectively, p=0.0006). Alcaftadine also showed lower mean itching scores over all time points (0.68 vs. 0.92 respectively, p=0.0390) compared with olopatadine. Finally, minimal itching (a score <1) was reported in 76.1 percent of alcaftadine-treated subjects versus 58.1 percent of olopatadine-treated subjects (p=0.0121).

**Ongoing Trials**

To round out these published offerings, let’s look at which studies have been posted to clinicaltrials.gov.

---

**GET THE 2015 HIRING GUIDE FOR**

**OPTOMETRY**  
**OPHTHALMOLOGY**  
**OPTICAL**

Download Your Free Hiring Guide Online at localeyesite.com/guide
In 2014, Nicox bought Aciex, and with it the rights to the antihistamine, cetirizine ophthalmic solution (AC-170), which has been evaluated in two pivotal CAC studies. Nicox’s website states that successful pre-NDA meetings have been held with the Food and Drug Administration, and that a submission date of the NDA will be announced in the near future. Ocular Therapeutix has developed technology for encapsulating ophthalmic pharmaceuticals within a hydrogel to deliver sustained therapeutic levels of various drugs via punctal plugs. One of these, OTX-DP, is a dexamethasone depot that has been tested for treatment of chronic allergic conjunctivitis modeled by multiple CACs.

Alcon has developed a high-dose olopatadine 0.77%, and results of an Alcon-sponsored CAC trial were presented at the ARVO meeting last year (clinicaltrials.gov: NCT01743027). This formulation appears to have benefits to controlling itching at 24 hours that the 0.2% olopatadine concentration doesn’t have. This high-dose olopatadine, named Pazeo, was just approved by the FDA in February 2015.

Eleven Biotherapeutics has completed a study on one of its lead candidate products, an interleukin-1 receptor antagonist, in a clinical model of moderate to severe allergic conjunctivitis using both an environmental exposure and modified conjunctival allergen provocation test (clinicaltrials.gov: NCT02082599). The company recently announced that the primary endpoint of ocular itching wasn’t demonstrated in the CAPT model.

Ultimately, reviewing the numerous reports on ocular allergy has shown us that interest in the topic is still very high, and has allowed us to draw some conclusions. Conventional immunomodulators like cyclosporine are being investigated anew for allergy; however, it’s uncertain if the efficacy of this class compares favorably to the previous generation of mast cell stabilizing/antihistaminic drugs. At the same time, chronic allergic diseases such as VKC and AKC are still challenging clinicians. Elsewhere in the treatment realm, ocular anti-allergics are continually being compared to highlight possible benefits of one over the other, while alcaftadine (Lastacaft) is proving to be very effective in numerous cases of ocular allergy. REVIEW

Dr. Abelson is trustee of the Schepens Eye Research Institute, emeritus surgeon of the Massachusetts Eye and Ear Infirmary, and clinical professor of ophthalmology at Harvard Medical School. Ms. Smith is a medical writer at Ora Inc.
Ono SJ, Lane K. Comparison of effects of alcaftadine and olopatadine on conjunctival epithelium and long acting H1-selective histamine antagonist and anti-allergic agent for use in allergic conjunctivitis. J


Olopatadine 0.2% in allergic conjunctivitis: pooled analysis of two multicenter randomized clinical trials. 29. McLaurin E, Marsico N, Ackerman S, Ciolino J, et al. Ocular itch relief with alcaftadine 0.25% versus epinastine 0.05% ophthalmic solution for treating itching and redness induced by conjunctival allergen challenge model. Acta Ophthalmol Scan Suppl 2000;230:60-63.


Abelson MB, Welch DL. An evaluation of onset and duration of action of Patanol (Olopatadine hydrochloride 0.1%) compared to Claritin (loratadine 10 mg) tablets in acute allergic conjunctivitis patients with nasal allergy. Allergy Proc 2013;34:3:247-254.


Mish FS, Rosenwater LJ, Townsend WD, Greiner JV, Borsch G. Efficacy and comfort of Olopatadine 0.2% versus epinastine 0.05% ophthalmic solution for treating itching and redness induced by conjunctival allergen challenge. Curr Med Res Opin 2007;23:6:1445-52.


Celik T, Turkoglu BB. Comparative evaluation of olopatadine 0.1% combined ketorolac 0.4% treatment versus olopatadine 0.1% combined ketorolac 0.4% treatment in patients with acute seasonal allergic conjunctivitis. Curr Eye Res 2014;39:1:42-6.


Muller GG, Jose NK, deCastro RS. Topical tacrolimus 0.03% as sole therapy in viral keratoconjunctivitis: a randomized double-masked study. Eye Contact Lens 2014;40:79-83.

