Double-Masked, Randomized, Parallel-Group Study Comparing Olopatadine 0.1% Ophthalmic Solution with Cromolyn Sodium 2% and Levocabastine 0.05% Ophthalmic Preparations in Children with Seasonal Allergic Conjunctivitis

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ABSTRACT

Background: It is estimated that >50% of medications have not been tested in children. Physicians need pediatric data to guide them in treating children. Olopatadine hydrochloride ophthalmic solution 0.1% is a topical antiallergic agent that is both an antihistamine with high affinity and selectivity for the histamine H₁ receptor and a mast cell stabilizer that inhibits the release of histamine and other proinflammatory mediators from human conjunctival mast cells. The efficacy and tolerability of olopatadine has been demonstrated by comparative studies in adults and children with seasonal allergic conjunctivitis (SAC).

Objective: Pediatric patient data were extracted from 2 clinical trials to assess the efficacy and tolerability of olopatadine hydrochloride ophthalmic solution 0.1% compared with those of cromolyn sodium ophthalmic solution 2% and levocabastine ophthalmic solution 0.05% as treatment for SAC in children.

Methods: In study 1, conducted at 15 centers in 7 countries (Europe and Australia) from October 1995 to December 1997, olopatadine was instilled BID and placebo (vehicle) BID for 6 weeks and compared with cromolyn instilled QID. Study 2, conducted at 17 centers in 8 countries (Europe and Australia) from November 1998 to June 2000, compared olopatadine BID with levocabastine BID. In both studies, children of either sex and any race, aged 4 to 11 years, and having proven grass pollen allergies were assigned to treatment in a double-masked, randomized fashion. Slit-lamp examination, the physician's im-

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pression scale, and self-ratings were used to obtain efficacy data. Data analyses were based on pollen concentrations. The tolerability assessments were based on visual acuity, pupil diameter, intraocular pressure, and a dilated fundus examination.

Results: Study 1 comprised 30 children (olopatadine [n = 13] and cromolyn sodium [n = 17]; 18 boys, 12 girls; mean age, 7.9 years [range, 4–11 years]). Study 2 comprised 22 children (olopatadine [n = 10] and levocabastine [n = 12]; 12 boys, 10 girls; mean age, 8.6 years [range, 5–11 years]). In study 1, ocular itching ($P = 0.010$), redness seen on slit-lamp examination ($P = 0.003$), and eyelid swelling ($P = 0.034$) were significantly less intense with olopatadine than with cromolyn sodium during the peak pollen period. In study 2, redness seen on slit-lamp examination ($P = 0.040$) and self-rated ocular redness ($P = 0.024$) were significantly less intense with olopatadine than levocabastine during the peak pollen period. Olopatadine was well tolerated.

Conclusion: Olopatadine hydrochloride ophthalmic solution 0.1% was more effective than both cromolyn sodium 2% and levocabastine 0.05% ophthalmic preparations in controlling ocular signs and symptoms of SAC in children and was well tolerated when administered twice daily for 6 weeks. (*Curr Ther Res Clin Exp.* 2004;65:186–199) Copyright © 2004 Excerpta Medica, Inc.

Key words: seasonal allergic rhinoconjunctivitis, eye drops, olopatadine, placebo, levocabastine, cromolyn sodium.

INTRODUCTION

It is estimated that >50% of medications used in children have never been tested in children.¹ Most data relevant to medications administered to children are derived from studies in adults. Physicians need pediatric data to guide them in treating children. This report describes a post hoc analysis of pediatric data from 2 trials of olopatadine hydrochloride ophthalmic solution 0.1% in seasonal allergic conjunctivitis (SAC) to provide further clinical pharmacologic data relevant to children.

Olopatadine hydrochloride ophthalmic solution 0.1%* is a topical antiallergic agent that is both an antihistamine with high affinity and selectivity for the histamine H₁ receptor and a mast cell stabilizer that inhibits the release of histamine and other proinflammatory mediators from human conjunctival mast cells.^{2,3} Olopatadine is active in the conjunctival allergen challenge model and has a rapid onset of action (within 20 minutes after instillation) and a duration of ≥ 8 hours.^{4–6} The efficacy of olopatadine has been demonstrated by comparative studies in patients with SAC and rhinoconjunctivitis; the agent was well tolerated when administered BID for 2 weeks.^{6–9}

*Trademark: Patanol® (US and Canada) or Opatanol® (Europe) (Alcon Laboratories Inc., Fort Worth, Texas).

The 2 studies reported here are based on 2 original trials^{8,9} that included both pediatric and adult patients (trial 1, N = 185 [155 adults, 30 children]; trial 2, N = 211 [189 adults, 22 children]). Trial 1, conducted at 15 centers in 7 countries (Europe and Australia) from October 1995 to December 1997, compared olopatadine hydrochloride ophthalmic solution 0.1% with cromolyn sodium 2% ophthalmic solution* in patients with SAC.⁸ When the trial was designed, cromolyn sodium was one of the most widely used mast cell inhibitors in Europe for the treatment of allergic ocular disease. Trial 2, conducted at 17 centers in 8 countries (Europe and Australia) from November 1998 to June 2000, compared olopatadine with levocabastine ophthalmic solution[†] in patients with SAC.⁹ Levocabastine is a second-generation histamine H₁ receptor antagonist that is marketed in several countries for the treatment of allergic conjunctivitis. A refinement of the methodology was used to correlate symptoms with concurrent pollen concentrations.^{10,11} Both trials, with all patients included, yielded statistically significant differences between their respective treatment groups, in favor of olopatadine.

In addition, both trials reported a statistically measurable interaction between treatment efficacy and age (all age groups). The interaction ($P = 0.002$) in trial 1 can be explained by a greater reduction of redness seen on slit-lamp examination in children aged ≤ 11 years treated with olopatadine; the reduction was almost 50% greater than in children treated with cromolyn sodium. In trial 2, a treatment-by-age interaction was also noted for itching, but the difference did not reach statistical significance. The interaction ($P = 0.042$) for redness seen on slit-lamp examination in trial 2 was also attributed to a greater reduction of redness in children aged ≤ 11 years treated with olopatadine compared with levocabastine. This finding suggested a greater therapeutic response to olopatadine in children. Therefore, we conducted this post hoc analysis to identify potential treatment effects in this group of patients.

PATIENTS AND METHODS

Patients

Children of either sex and any race aged 4 to 11 years were eligible for the studies if they met the following requirements: (1) a history of SAC lasting ≥ 1 allergy season (study 2 also included patients with rhinoconjunctivitis and the possible complication of mild asthma controlled by bronchodilators); (2) positive skin reactions to common local grass pollens, including Gramineae, at screening or in the 12 months before the study; and (3) a current complaint of itching and conjunctival redness in both eyes.

Patients were excluded from the studies for the following reasons: another previous or ongoing ocular disorder; sensitivity to any component of the study medications; use of medication between 1 week before the study

*Trademark: Opticrom® (Fisons Pharmaceutical Division, Holmes Chapel, England).

†Trademark: Livostin™ (Janssen Pharmaceutica Products, LP, Beerse, Belgium).

and study completion that could confound the interpretation of results (eg, antihistamines other than the study drug, corticosteroids, nonsteroidal anti-inflammatory drugs, mast cell stabilizers, topical ocular vasoconstrictors); participation in other drug studies during the month before the study; and the inability to discontinue wearing contact lenses during the study.

Study 2 further excluded patients with visual acuity not correctable to ≥ 0.6 logMAR in both eyes, autoimmune disease associated with dry eye syndrome (eg, rheumatoid arthritis), or severe uncontrolled disease, and patients who used immunosuppressive drugs, sulfa- or neomycin-containing antibiotics, antibiotics to which they were sensitive, or tear substitutes. Patients receiving treatment with excluded concomitant medications had to discontinue these therapies ≥ 1 week before starting the study medication.

Ethical Conduct

Both original trials complied with the ethical principles of the Declaration of Helsinki applicable at the time (ie, 1989 for study 1 and 1997 for study 2). They were approved by the appropriate ethics committees, and written informed consent was obtained from legal guardians. Good clinical practice was observed throughout the trials.

Procedures

These double-masked, multicenter trials were conducted according to a parallel-group design that assigned treatments in equal ratio to sequential patients by a computer-generated randomization schedule. The target in each original trial was to enroll 200 patients to achieve ≥ 172 (trial 1) or 170 (trial 2) assessable patients.

Olopatadine hydrochloride ophthalmic solution 0.1% was instilled BID (morning and evening) in both studies. In study 1, placebo (olopatadine vehicle) was instilled BID (noon and afternoon), and the comparison treatment was cromolyn sodium ophthalmic solution QID (morning, noon, afternoon, and evening). The comparator drug in study 2 was levocabastine ophthalmic suspension 0.05% BID (morning and evening). Treatments in both studies continued for 6 weeks. Identical opaque Drop-Tainer bottles (Alcon-Couvreur SA, Puurs, Belgium) and labels ensured adequate masking of treatment assignment. Standardized administration technique required the child's guardian to retract the lower eyelid and instill 1 drop of study drug bilaterally (if the first attempt failed, a second drop was administered). Previous medication for SAC was discontinued at the screening visit, and a washout period of ≥ 1 week was required prior to starting study drug. Paracetamol and pseudoephedrine hydrochloride were allowed during the studies. Clinic visits were scheduled for days 0 (randomization and start of study treatment), 3, 7, 14, 30, and 42 (last day of treatment). A final visit followed 2 to 3 days later. Study 2 also allowed topical treatments, such as mometasone nasal spray or inhaled beta₂-adrenergic agonists, and maintenance immunotherapy (at doses stabilized ≥ 3 months prior to the study).

Primary efficacy variables comprised ocular itching and conjunctival redness. Itching was self-rated at each visit. Investigators asked patients, "How often during the last 3 days did your eyes itch enough that you wanted to rub them?" Replies were rated at 5 frequency levels: 0 = none, 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = very frequently. In addition, investigators rated conjunctival redness (redness on slit-lamp examination compared with standard reference photographs) at 9 levels (scored in 0.5-U increments from 0–4), with each level defined (0 = baseline, no dilatation of vessels, to 4 = beefy, tomato-red vessels; total involvement of all quadrants and straight through to the limbus 360°).

Secondary efficacy variables comprised chemosis and eyelid swelling (assessed by slit-lamp examination and rated as above). Study 2 also included patient self-ratings of ocular redness and nasal symptoms elicited at interview by physicians. Investigators also compared the patient's overall clinical condition at each visit to that at study entry and rated change (Physicians' Impression Scale) at 6 levels: 0 = clinical cure, 1 = satisfactory clinical response, 2 = slight clinical improvement, 3 = clinically unchanged, 4 = slightly clinically worse, and 5 = significantly clinically worse. Levels were defined in terms of medication need. Patients of both studies kept a diary and self-rated the intensity of ocular itching and redness, each on a 10-point scale ranging from 0 = none to 9 = severe. Younger patients kept the diary and completed it with parents' assistance. Study 2 specified symptom intensity as being that of the most severe episode since the previous evening. Measures of efficacy reflected the disease state; transient reactions to instillation of medication were reported as adverse events (AEs).

Grain counts of the most common grass pollens were obtained daily from local pollen collection stations. A pollen allergy profile specific to each patient was compiled in study 1; mean grain counts/pollen type during the 7 days prior to office visits were recorded for every patient in study 2.

Tolerability data included AEs and ocular changes. AEs were defined as clinically relevant changes from baseline (expected or unexpected) that excluded events related only to disease progression (eg, signs and symptoms of allergy) or to concomitant illness. Investigators rated AEs in relation to treatments as follows: 1 = definitely unrelated, 2 = unlikely, 3 = possible, 4 = probable, and 5 = definitely related. Ocular examinations (on day 0 and the final visit) comprised visual acuity, intraocular pressure (IOP), and nondilated fundus appearance. Also, investigators assessed each patient regularly and withdrew him or her from the study if his or her allergic symptoms were not adequately controlled (treatment failure).

Statistical Analysis

The post hoc statistical objective of the 2 studies reported was to compare the efficacy of olopatadine with cromolyn sodium and levocabastine. All patients who received medication were assessed by intent-to-treat (ITT) efficacy and

tolerability analyses. Data were not imputed for study 1, although data from the last visit were carried forward for patients withdrawn from study 2 but were not imputed for the tolerability analyses. No correction for multiplicity was made in these post hoc analyses. It was not possible in either study to distinguish between treatment failure and poor treatment compliance; hence, either outcome was classified as *treatment failure*. Treatment comparisons and changes from baseline were assessed using 2-sample *t* tests applied to the mean values of variables during peak and declining pollen periods. Demographic comparisons between treatment groups used a 2-sample *t* test or Fisher exact test. Tolerability analyses used Fisher exact test for changes in visual acuity, a 2-sample *t* test for IOP changes, and repeated-measures analysis of variance for pupil diameter changes. All statistical analyses were performed using SAS software version 6.12 (SAS Institute Inc., Cary, North Carolina). Statistical significance was set at $P \leq 0.05$.

RESULTS

Efficacy

Study 1

Treatments were randomized among 188 patients, including 30 children. All children received treatment; consequently, 30 children (olopatadine, $n = 13$; cromolyn sodium, $n = 17$) were assessed by the ITT efficacy and tolerability analyses. Major protocol violations were recorded for 2 children—one in the olopatadine group did not meet the selection criteria for symptoms in both eyes and one in the cromolyn sodium group had a negative skin test result. The baseline demographic characteristics did not differ significantly between the olopatadine and cromolyn groups (boys, 9 and 9 patients, respectively; girls, 4 and 8 patients, respectively; mean [SD] ages, 7.2 [1.6] and 8.5 [1.8] years, respectively).

Gramineae pollens were abundant at every site and were the most common cause of allergy. At baseline screening, 26 (86.7%) of 30 children reacted positively to them. The **figure** shows the data that were obtained during the season of Gramineae pollen release. Mean Gramineae counts remained close to the baseline level during treatment visits on days 3, 7, and 14 (peak pollen period) and then decreased on treatment days 30 to 42 (declining pollen period). The mean data obtained during the peak period were analyzed separately from the means obtained during the declining period.

Ocular assessments at baseline did not differ significantly between treatment groups (**Table I**). However, during the peak pollen period, the primary efficacy variables—ocular itching and conjunctival redness assessed using slit-lamp examination—were significantly less with olopatadine than with cromolyn sodium ($P = 0.010$ and $P = 0.003$, respectively). A similar result was obtained with the secondary efficacy variable of eyelid swelling ($P = 0.034$). No significant differences were noted between treatments for chemosis, assessed using slit-lamp examination. Overall clinical change from baseline, as rated on the Phy-

Figure. Mean (SEM) Gramineae pollen count throughout the 2 studies. Data for study 2, day 3 are unavailable.

sician's Impression Scale, was significantly better for olopatadine than cromolyn sodium during the peak pollen period ($P = 0.003$), which was consistent with the preceding results. These significant differences were maintained during the declining pollen period, except as rated on the Physician's Impression Scale.

Patients' diary entries showed somewhat lower scores for ocular itching and redness with olopatadine treatment than with cromolyn sodium, but the only significant difference was for ocular redness during the declining pollen period ($P = 0.019$). All symptoms decreased significantly relative to baseline values with both treatments during both the peak and declining pollen periods (all $P < 0.05$), except for diary (self-rated) ocular itching and redness with cromolyn sodium during the peak pollen period.

Study 2

Treatments were randomized among 211 patients, including 22 children. All children received treatment; consequently, 22 children (olopatadine, $n = 10$; levocabastine, $n = 12$) were included in the ITT efficacy and tolerability analyses. Two children were not assessable due to major protocol violations (did not meet the selection criteria [$n = 1$ in the levocabastine group] and did not return for assessment [$n = 1$ in the olopatadine group]). Three additional children withdrew from the study (olopatadine [patient decision, $n = 1$] and levocabastine [treatment failure, $n = 2$]). The baseline demographic characteristics did not differ significantly between the olopatadine and levocabastine groups

Table I. Ocular symptoms and signs, Physician's Impression Scale ratings, and diary self-ratings of ocular symptoms in study 1 (N = 30).

Parameter/Study Drug	Baseline	Peak Pollen Period	Declining Pollen Period
Symptoms and signs			
Primary efficacy variables			
Itching, self-rated*			
Olopatadine 0.1%	3.96	1.95 [†]	0.92 [†]
Cromolyn sodium 2%	4.00	3.08 [†]	2.41 [†]
<i>p</i> [‡]	0.337	0.010	0.010
Redness, on slit-lamp examination [§]			
Olopatadine 0.1%	2.62	1.04 [†]	0.64 [†]
Cromolyn sodium 2%	2.90	1.90 [†]	1.56 [†]
<i>p</i> [‡]	0.187	0.003	0.013
Secondary efficacy variables			
Chemosis, on slit-lamp examination			
Olopatadine 0.1%	1.35	0.49 [†]	0.29 [†]
Cromolyn sodium 2%	1.41	0.95 [†]	0.49 [†]
<i>p</i> [‡]	0.874	0.100	0.367
Eyelid swelling, on slit-lamp examination [¶]			
Olopatadine 0.1%	1.15	0.37 [†]	0.10 [†]
Cromolyn sodium 2%	1.59	0.93 [†]	0.51 [†]
<i>p</i> [‡]	0.238	0.034	0.032
Physician's Impression Scale [#] ratings (change scores)			
Olopatadine 0.1%	–	1.23	0.83
Cromolyn sodium 2%	–	1.98	1.47
<i>p</i> [‡]	–	0.003	0.091
Diary self-ratings			
Itching, diary ^{**}			
Olopatadine 0.1%	5.33	2.47 [†]	1.36 [†]
Cromolyn sodium 2%	4.41	3.39	2.31 [†]
<i>p</i> [‡]	0.254	0.215	0.159
Redness, diary ^{**}			
Olopatadine 0.1%	4.67	3.31 [†]	1.77 [†]
Cromolyn sodium 2%	4.41	4.21	3.29 [†]
<i>p</i> [‡]	0.718	0.192	0.019

*Response to the question, "How often during the last 3 days did your eyes itch enough that you wanted to rub them?" Scale: 0 = none, 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = very frequently.

[†]*P* < 0.05 versus day 0 (*t* test).

[‡]Between-treatment difference (*t* tests, assuming homogeneous variance).

[§]Scale: 0 = baseline, no dilatation of vessels, to 4.0 = beefy, tomato-red vessels; total involvement of all quadrants and straight through to the limbus 360°.

^{||}Scale: 0 = none, to 4.0 = severe overall ballooning of conjunctiva.

[¶]Scale: 0 = none, to 4.0 = lid closure.

[#]Scale: 0 = clinical cure, 1 = satisfactory clinical response, 2 = slight clinical improvement, 3 = clinically unchanged, 4 = slightly clinically worse, and 5 = significantly clinically worse.

^{**}Scale: 0 = none, to 9 = severe.

(boys, 4 and 8 patients, respectively; girls, 6 and 4 patients, respectively; mean [SD] age, 8.3 [1.7] and 8.8 [1.8] years, respectively).

Gramineae pollens were abundant at every site and represented the most common cause of allergy. At baseline, 19 of 22 children (86.4%) reacted positively to them. The figure shows that the study was conducted during the Gramineae pollen season. The mean Gramineae counts remained close to the baseline level during the treatment visit on day 7 (peak pollen period) and then decreased on treatment days 14 to 42 (declining pollen period). The means obtained during the peak period were analyzed separately from the means obtained during the declining period.

Ocular assessments at baseline did not differ significantly between treatment groups (**Table II**). However, during the peak pollen period, the primary efficacy variable of conjunctival redness was significantly lower with olopatadine than levocabastine 0.05% treatment ($P = 0.040$). A similar result was obtained with the secondary efficacy variable of self-rated ocular redness ($P = 0.024$). Overall clinical change from baseline, as rated on the Physician's Impression Scale, showed the olopatadine change score to be significantly better than that of levocabastine during the peak pollen period ($P = 0.026$). These significant differences were maintained during the declining pollen period and extended to ocular itching ($P = 0.029$) and eyelid swelling ($P = 0.050$).

Patients' diary records showed scores for ocular itching and redness that were similar between treatments at peak pollen count, but during the declining pollen period the score for ocular itching was significantly lower with olopatadine compared with levocabastine ($P = 0.031$).

With olopatadine, all symptoms except eyelid swelling decreased significantly from baseline values during both the peak and declining pollen periods (all $P < 0.05$). In contrast, with levocabastine, itching rated at interview and both itching and redness diary self-ratings decreased significantly from baseline during the peak and declining pollen periods (all $P < 0.05$), but self-rated redness and chemosis decreased significantly from baseline only during the declining pollen period (both $P < 0.05$), and eyelid swelling did not decrease significantly during either period.

No significant changes were observed in nasal symptoms and signs from baseline in pediatric patients following ocular instillation of olopatadine or levocabastine.

Tolerability

Considering both studies together, 9 children experienced 10 AEs. In the patients receiving olopatadine 0.1%, 1 case each of the following AEs was reported once: ocular discharge, keratitis, fever, and rhinitis. In the patients receiving levocabastine 0.05%, 1 case of vomiting was reported. In the patients receiving cromolyn sodium 2%, 1 case of each of the following AEs was reported: conjunctivitis, ocular redness, ocular accident injury, fever, and pneumonia. None of the AEs were serious and none of the children were discontinued from

Table II. Ocular symptoms and signs, Physician's Impression Scale ratings, and diary self-ratings of ocular symptoms in study 2 (N = 22).

Parameter/Study Drug	Baseline	Peak Pollen Period	Declining Pollen Period
Symptoms and signs			
Primary efficacy variables			
Itching, self-rated*			
Olopatadine 0.1%	4.30	2.40 [†]	1.00 [†]
Levocabastine 0.05%	4.42	3.04 [†]	2.28 [†]
<i>p</i> [‡]	0.651	0.209	0.029
Redness, on slit-lamp examination [§]			
Olopatadine 0.1%	2.20	0.95 [†]	0.53 [†]
Levocabastine 0.05%	2.71	1.77 [†]	1.33 [†]
<i>p</i> [‡]	0.254	0.040	0.032
Secondary efficacy variables			
Redness, self-rated*			
Olopatadine 0.1%	3.90	1.40 [†]	0.70 [†]
Levocabastine 0.05%	3.58	2.88	2.15 [†]
<i>p</i> [‡]	0.552	0.024	0.021
Chemosis, on slit-lamp examination			
Olopatadine 0.1%	1.05	0.30 [†]	0.17 [†]
Levocabastine 0.05%	1.42	0.92	0.51 [†]
<i>p</i> [‡]	0.507	0.128	0.167
Eyelid swelling, on slit-lamp examination [¶]			
Olopatadine 0.1%	0.90	0.15	0.00 [†]
Levocabastine 0.05%	1.17	0.88	0.48
<i>p</i> [‡]	0.626	0.055	0.050
Physician's Impression Scale [#] ratings (change scores)			
Olopatadine 0.1%	–	1.10	0.57
Levocabastine 0.05%	–	2.08	1.67
<i>p</i> [‡]	–	0.026	0.026
Diary self-ratings			
Itching, diary**			
Olopatadine 0.1%	5.80	1.83 [†]	0.96 [†]
Levocabastine 0.05%	5.42	3.41 [†]	2.56 [†]
<i>p</i> [‡]	0.724	0.052	0.031
Redness, diary**			
Olopatadine 0.1%	5.00	2.72 [†]	1.84 [†]
Levocabastine 0.05%	5.42	4.03 [†]	3.25 [†]
<i>p</i> [‡]	0.634	0.116	0.140

*Response to the question "How often during the last 3 days did your eyes itch enough that you wanted to rub them?" Scale: 0 = none, 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = very frequently.

[†] $P < 0.05$ versus day 0 (*t* test).

[‡]Between-treatment difference (*t* tests, assuming homogeneous variance).

[§]Scale: 0 = baseline, no dilatation of vessels, to 4.0 = beefy, tomato-red vessels; total involvement of all quadrants and straight through to the limbus 360°.

^{||}Scale: 0 = none, to 4.0 = severe overall ballooning of conjunctiva.

[¶]Scale: 0 = none, to 4.0 = lid closure.

[#]Scale: 0 = clinical cure, 1 = satisfactory clinical response, 2 = slight clinical improvement, 3 = clinically unchanged, 4 = slightly clinically worse, and 5 = significantly clinically worse.

^{**}Scale: 0 = none, to 9 = severe.

therapy due to an AE. Only 1 AE, a mild ocular discharge, was considered to be related to treatment (olopatadine). Also, all changes from baseline in visual acuity, pupil diameter, IOP (≥ 10 mm Hg), and undilated fundus parameters were clinically unimportant. All 3 treatments were well tolerated.

DISCUSSION

Data from both original trials^{8,9} were reanalyzed post hoc to extract information on potential treatment effects in children. A number of caveats apply to the repeat analyses. In the original trials, treatments were masked and randomized in equal ratio to sequential patients who were not stratified by age. As a consequence, the treatments were not truly randomized for the pediatric subpopulations. Also, the power calculations made for both original trials (power >90% with 85 patients per treatment group) did not apply only to the recruitment of children. These shortcomings, however, do not invalidate the present exploratory findings obtained in 2 independent studies.

The original statistical analysis of trial 1 was designed to compare the efficacies of olopatadine and cromolyn sodium, and the analysis of trial 2 was designed to compare the efficacies of olopatadine and levocabastine. The original trials were analyzed as planned (treatment comparisons at each visit). By contrast, the present pediatric analyses simply applied 2-sample *t* tests to studies 1 and 2. Also, the means were calculated during peak and declining pollen counts to reduce type 1 errors that would increase with numerous statistical comparisons. However, an unavoidable result of such averaging is smoothed data and a loss of detail. On the other hand, the purpose of the post hoc analyses was to identify potential treatment effects in pediatric patients. The consistency of the results within and between the studies suggests that spurious significant effects were not problematic.

The fact that both studies excluded patients with ocular disorders that a priori might have invalidated subsequent assessments could limit generalizations from the reported results. However, SAC accounts for more than half of all ocular allergy cases, and many patients suffer ocular symptoms only, as did most patients in the present samples.^{7,12,13} The present methodologic concerns would not normally arise in routine clinical practice.

Two crucial aspects of both studies were recruiting only patients with positive skin reactions to common grass pollens and having pollen counts for the times when patients were being assessed. Pollen counts were similar for the 2 studies. The peak and declining pollen periods were distinct in both studies, and these distinct pollen periods were used to partition the data. The justification for this was the study by Abelson and Turner,⁶ which showed a relationship between pollen counts and symptoms of seasonal allergic rhinoconjunctivitis. In that study, the authors showed that the proportion of patients with frequent ocular itching and redness during placebo administration in-

creased as a function of pollen counts. With olopatadine treatment, the proportion of patients with frequent ocular itching and redness was comparable to that found at the lowest pollen count.

The treatment differences in children with SAC were consistent and showed olopatadine to be more effective than either comparison treatment. During peak pollen periods, olopatadine was significantly more effective than cromolyn sodium in terms of ocular itching, redness on slit-lamp examination, eyelid swelling, and the Physician's Impression Scale (all $P < 0.05$). Also during peak pollen periods, olopatadine was more effective than levocabastine with respect to self-rated redness, redness on slit-lamp examination, and the Physician's Impression Scale (all $P < 0.05$). Moreover, as pollen counts declined, olopatadine continued to be significantly more effective than cromolyn sodium (ie, ocular itching, redness on slit-lamp examination, and eyelid swelling; all $P < 0.05$). It also remained more effective than levocabastine in terms of self-rated redness, redness on slit-lamp examination, the Physician's Impression Scale, ocular itching, and eyelid swelling (all $P \leq 0.05$). Olopatadine was not less effective than either cromolyn sodium or levocabastine in any case.

In both studies, all changes from baseline with olopatadine for primary and secondary variables (excluding eyelid swelling in study 2 and physician impression in both studies) were significant at all times (all $P < 0.05$), during peak and declining pollen counts. With cromolyn sodium, however, certain changes from baseline (diary records of ocular itching and redness) became significant only when pollen counts declined ($P < 0.05$). The same applied to levocabastine with respect to self-rated redness and chemosis. Therefore, it seems reasonable to infer that declining pollen counts could influence therapeutic drug effects in 2 ways—moderate pollen counts might reveal weak therapeutic effects and sufficiently low counts would obviate therapy.

The results are consistent with those found in the original trials,^{8,9} in which interactions between the present treatments and age (all age groups) demonstrated greater benefits with olopatadine in young children. All 3 treatments were well tolerated by the children in the present studies.

Despite the obvious shortcomings of post hoc analyses and the small number of children observed, the consistent findings within and between the 2 independent studies demonstrated the clinical relevance and tolerability of olopatadine in children with SAC. This information will be helpful to physicians when they consider treatment options in children.

The present findings may be compared to those of 4 previously published trials^{14–17} in children and adolescents with SAC and seasonal allergic rhinoconjunctivitis. Two of these trials^{14,15} showed patient global ratings for levocabastine 0.05% eye drops BID to be higher than those for cromoglycate sodium 2% eye drops QID ($P < 0.05$). The third trial¹⁶ compared nedocromil sodium 2% eye drops (BID) with vehicle (control). The significance of the fourth trial¹⁷ was that nedocromil sodium 2% BID was found to be similar to cromoglycate sodium 2% QID. Nedocromil significantly reduced ocular itching and watering and

total symptom scores (all $P < 0.05$).¹⁷ The respective treatments were well tolerated in all 4 studies.

The present preliminary results with olopatadine 0.1% in children with SAC need to be replicated in a larger-scale prospective study that similarly takes into account pollen concentrations.

CONCLUSION

Olopatadine hydrochloride ophthalmic solution 0.1% was more effective than both cromolyn sodium 2% and levocabastine 0.05% ophthalmic preparations in controlling ocular signs and symptoms of SAC in children and is well tolerated when administered twice daily for 6 weeks.

REFERENCES

1. European Commission Enterprise Directorate-General. Better Medicines for children: Proposed regulatory actions on paediatric medicinal products. Consultation Document. *Int J Pharm Med.* 2002;16:25–29.
2. Sharif NA, Xu SX, Miller ST, et al. Characterization of the ocular antiallergic and antihistaminic effects of olopatadine (AL-4943A), a novel drug for treating ocular allergic diseases. *J Pharmacol Exp Ther.* 1996;278:1252–1261.
3. Yanni JM, Stephens DJ, Miller ST, et al. The in vitro and in vivo ocular pharmacology of olopatadine (AL-4943A), an effective anti-allergic/antihistaminic agent. *J Ocul Pharmacol Ther.* 1996;12:389–400.
4. Butrus S, Greiner JV, Discepolo M, Finegold I. Comparison of the clinical efficacy and comfort of olopatadine hydrochloride 0.1% ophthalmic solution and nedocromil sodium 2% ophthalmic solution in the human conjunctival allergen challenge model. *Clin Ther.* 2000;22:1462–1472.
5. Abelson MB, Spitalny L. Combined analysis of two studies using the conjunctival allergen challenge model to evaluate olopatadine hydrochloride, a new ophthalmic antiallergic agent with dual activity. *Am J Ophthalmol.* 1998;125:797–804.
6. Abelson MB, Turner D. A randomized, double-blind, parallel-group comparison of olopatadine 0.1% ophthalmic solution versus placebo for controlling the signs and symptoms of seasonal allergic conjunctivitis and rhinoconjunctivitis. *Clin Ther.* 2003; 25:931–946.
7. Aguilar AJ. Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. *Acta Ophthalmol Scand Suppl.* 2000;(230):52–55.
8. Katelaris CH, Ciprandi G, Missotten L, et al, for the International Olopatadine Study Group. A comparison of the efficacy and tolerability of olopatadine hydrochloride 0.1% ophthalmic solution and cromolyn sodium 2% ophthalmic solution in seasonal allergic conjunctivitis. *Clin Ther.* 2002;10:1561–1575.
9. Bertin D, Fedrigo A, Cano-Parra J, for the International Patanol Clinical Group. Efficacy and safety of olopatadine (PATANOL®) eye drops 0.1% compared to levocabastine 0.05% in seasonal allergic conjunctivitis. *Ophthalm Res.* EVER 2001—Abstracts, September 2001, Supplement. Abstract 3201.
10. Milliken GA, Johnson DE. *Analysis of Messy Data.* Vol 1. London: Chapman Hall; 1994.

11. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. *SAS System for Mixed Models*. 1996;5.4.2.
12. Friedlaender MH. Current concepts in ocular allergy. *Ann Allergy*. 1991;67:5–10, 13.
13. Hordijk GJ, Antvelink JB, Luwema RA. Sublingual immunotherapy with a standardised grass pollen extract; a double-blind placebo-controlled study. *Allergol Immunopathol (Madrid)*. 1998;26:234–240.
14. Odelram H, Björkstén B, af Klercker T, et al. Topical levocabastine versus sodium cromoglycate in allergic conjunctivitis. *Allergy*. 1989;44:432–436.
15. Vermeulen J, Mercer M. Comparison of the efficacy and tolerability of topical levocabastine and sodium cromoglycate in the treatment of seasonal allergic rhinoconjunctivitis in children. *Paediatr Allergy Immunol*. 1994;5:209–213.
16. Möller C, Berg IM, Berg T, et al. Nedocromil sodium 2% eye drops for twice-daily treatment of seasonal allergic conjunctivitis: A Swedish multicentre placebo-controlled study in children allergic to birch pollen. *Clin Exp Allergy*. 1994;24:884–887.
17. Leino M, Ennevaara K, Latvala AL, et al. Double-blind group comparative study of 2% nedocromil sodium eye drops with 2% sodium cromoglycate and placebo eye drops in the treatment of seasonal allergic conjunctivitis. *Clin Exp Allergy*. 1992;22:929–932.

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