Objective: To evaluate the effects on signs and symptoms of a coexisting vernal keratoconjunctivitis in patients treated with oral montelukast sodium for asthma.

Methods: Twelve patients with vernal keratoconjunctivitis and asthma were enrolled in this pilot study. Topical eyedrops or any systemic treatment was discontinued for at least 7 days before montelukast treatment. Patients were asked to grade their ocular discomfort daily. The following signs and symptoms were also recorded and graded through medical examination at baseline, after 15 days of treatment, and 15 days after treatment discontinuation: physician-evaluated tarsal and bulbar papillae, hyperemia, secretion, and chemosis; and patient-evaluated itching, burning, tearing, photophobia, foreign body sensation, secretion, and redness. Peak expiratory flow rate at 8 AM was also recorded. Samples were collected at the same time points for enzyme-linked immunosorbent assay measurement of leukotriene B4 in tears and leukotriene E4 in urine.

Results: Eight of the 10 patients evaluated reported a reduction in symptoms at the end of treatment. Montelukast treatment significantly decreased physician-rated hyperemia, secretion, and chemosis as well as patient-rated burning, tearing, photophobia, secretion, and redness. Effects persisted 15 days after discontinuation of treatment. Clinical changes were associated with a significant increase in leukotriene B4 in tears and a significant decrease in leukotriene E4 in urine after 15 days of treatment.

Conclusion: The significant and persistent reduction of ocular signs and symptoms in asthmatic patients with vernal keratoconjunctivitis treated for 15 days with montelukast strongly suggests the need for double-masked placebo-controlled trials to confirm the potential of this new treatment in vernal keratoconjunctivitis.

From the Interdisciplinary Research Center, University “Campus Bio-Medico,” Laboratory of Ophthalmology, Rome, Italy (Drs Lambiase, Stefano Bonini, Coassin, and Bruscolini); “G. B. Bietti” Eye Foundation, Rome (Drs Lambiase and Stefano Bonini); Institute of Neurobiology and Molecular Medicine, National Research Council, Rome (Dr Rasi and Sergio Bonini); and Department of Allergy and Clinical Immunology, II University of Naples, Naples, Italy (Dr Sergio Bonini). The authors have no relevant financial interest in this article.
persensitivity and inflammatory reactions. Their activities include smooth-muscle contraction, small-vessel dilation, increase in blood vessel permeability, promotion of glycoprotein secretion from epithelial glands, and increase in nasal blood flow and airway resistance.

Vernal keratoconjunctivitis is a rare but severe inflammatory disease of the eye that can represent a model of eosinophilic inflammation. No drug is at present available to fully achieve the ultimate goal of treatment, ie, control of the inflammatory process and symptoms as well as prevention of recurrences without significant adverse effects. In fact, topical corticosteroids represent the elective therapy for the acute phase of the disease, but they cannot be used for a prolonged period, because of severe and relatively common adverse effects (glaucoma and cataract). Other drugs (mast cell stabilizers, antihistamines, and nonsteroid anti-inflammatory drugs) have been used to treat VKC, but they are not able to completely control inflammation and symptoms in all patients. Further studies are therefore required to improve the management of this “orphan disease” (ie, a disease having an unclarified pathogenesis and no gold standard of treatment).

Montelukast sodium is an orally administered, specific cysteinyl LT receptor 1 antagonist that has been found to be effective in treatment of asthma. Recently, pilot studies have shown that montelukast might also have a role in the treatment of allergic rhinitis, nasal polyposis associated with asthma, chronic urticaria, and atopic dermatitis.

The goal of this pilot study was to evaluate the effects of montelukast in patients with VKC in whom this treatment was justified by the coexistent asthma, by observing the benefits induced by the drug on the ocular signs and symptoms.

This trial was approved by the Ethical Review Committee of the Fondazione G. B. Bietti, Rome, Italy, and performed in fully compliance with the requirements of local regulatory authorities and Good Clinical Practice standards. The study, performed in spring, involved 12 patients (11 males and 1 female; mean ± SD age, 15.7 ± 9.6 years; range, 4-31 years) with VKC (5 patients were symptomatic year-round, while 7 had symptoms only during spring) and mild asthma. All patients but one were positive for at least 1 common inhalant allergen, and all patients were symptomatic at the time they entered the study (April). All systemic and local treatments were discontinued for at least 1 week before montelukast treatment. The drug regimen included a 15-day trial of montelukast sodium (Singulair; Merck Sharp & Dohme, Whitehouse Station, NJ), 10 mg daily in adults and 5 mg daily in children. Patients were assessed at baseline, at the end of treatment, and 15 days after discontinuation of treatment. Patients were asked to fill a daily diary card that contained a daytime VKC symptom score and the measurement of peak expiratory flow rate at 8 AM. During the trial, β₂-agonists and antihistamine eyedrops were allowed as rescue treatment for asthma and VKC, respectively. Their use was recorded and evaluated as a sign of the efficacy of montelukast treatment. Two patients were not included in the final analysis because of poor compliance (failed to take the drug as instructed) (Table 1).

### OCULAR EVALUATION

Symptoms (itching, burning, tearing, photophobia, foreign body sensation, secretion, and redness) and signs (tarsal and bulbar papillae, hyperemia, secretion, and chemosis) were recorded and graded (from 0 to 3; 0, absent; 1, weak; 2, mild; and 3, severe) at each examination. Ocular examination was performed by slitlamp evaluation by the same physician (A.L.) at baseline and during the treatment. Peak expiratory flow rate was evaluated and tear and urine samples were collected at each examination.

### PEAK EXPIRATORY FLOW RATE

The peak expiratory flow rate was evaluated by a peak flow meter (Personal Best; Respironics, Inc, Murrysville, Pa) at 8 AM. Values were expressed as the percentage of the mean predicted value.

### LTE MEASUREMENT IN THE URINE

In our study we used urinary LTE₄ concentration as a marker of cysteinyl LT synthesis because it appears to be the predominant, stable, and consistent cysteinyl LT in urine. Urine samples were collected and stored at −80°C until use. Urinary LTE₄ was measured by a sensitive commercial immunosassay (Cayman Chemical Co, Ann Arbor, Mich) with the use of LTE₄ antiserum and acetylcholinesterase-linked LTE₄ tracer. Briefly, 50 µL of standard or unpurified urine sample (in several dilutions) was pipetted in duplicate into each well of a ready-to-use microtiter plate (96 wells) that was pre-

### METHODS

#### PEAK EXPIRATORY FLOW RATE

The peak expiratory flow rate was evaluated by a peak flow meter (Personal Best; Respironics, Inc, Murrysville, Pa) at 8 AM. Values were expressed as the percentage of the mean predicted value.

#### LTE MEASUREMENT IN THE URINE

In our study we used urinary LTE₄ concentration as a marker of cysteinyl LT synthesis because it appears to be the predominant, stable, and consistent cysteinyl LT in urine. Urine samples were collected and stored at −80°C until use. Urinary LTE₄ was measured by a sensitive commercial immunoassay (Cayman Chemical Co, Ann Arbor, Mich) with the use of LTE₄ antiserum and acetylcholinesterase-linked LTE₄ tracer. Briefly, 50 µL of standard or unpurified urine sample (in several dilutions) was pipetted in duplicate into each well of a ready-to-use microtiter plate (96 wells) that was pre-

### RESULTS

#### Peak Expiratory Flow Rate

The peak expiratory flow rate at 8 AM was determined before and during the trial. The values were expressed as percentages of the mean predicted value. During the trial, there was a significant increase in peak expiratory flow rate in all patients, as shown by the mean values at baseline, during the treatment, and 15 days after discontinuation of treatment (Table 2).

#### LTE Measurement in the Urine

Urine samples were collected and stored at −80°C until use. Urinary LTE₄ was measured by a sensitive commercial immunoassay (Cayman Chemical Co, Ann Arbor, Mich) with the use of LTE₄ antiserum and acetylcholinesterase-linked LTE₄ tracer. Briefly, 50 µL of standard or unpurified urine sample (in several dilutions) was pipetted in duplicate into each well of a ready-to-use microtiter plate (96 wells) that was pre-

### CONCLUSIONS

Montelukast sodium was effective in reducing the symptoms and signs of VKC in patients with allergic rhinitis, nasal polyposis, and mild asthma. The drug improved the peak expiratory flow rate and reduced the urinary LTE₄ concentration, suggesting that it may have a role in the treatment of VKC. Further studies are required to confirm these findings and to determine the optimal dosage and duration of montelukast treatment.
coated with mouse monoclonal antirabbit IgG. The enzyme-linked acetylcholinesterase tracer (50 µL) was then added to all of the wells except for the total activity and blank wells. The same volume of LTB4 antiserum was added to each well except the blank and nonspecific binding wells of a standard curve (standards ranging from 7.8 to 1000 pg/mL). The working detection limit of the assay was approximately 8 pg/mL.

**LTB4 MEASUREMENT IN TEARS**

We evaluated LTB4 concentration in the tears of patients with VKC, because this LT is the most studied one in allergic conjunctivitis and regarded as a marker of the inflammatory process.27,28 Tear samples were collected by capillary tubes and frozen at −80°C until the evaluation for LTB4 concentration by a specific enzyme-linked immunosorbent assay (Biotrak; Amersham Biosciences, Little Chalfont, England) according to the manufacturer's procedure. Briefly, 50 µL of each standard or tear sample and 50 µL of rabbit anti-LTB4 were added to all wells except the blank and nonspecific binding wells of a polystyrene 96-well immunoplate (NUNC A/S, Roskilde, Denmark) and incubated for 2 hours at room temperature on a microtiter plate shaker. After incubation, 50 µL of LTB4 peroxidase conjugate was added to all wells except the blank. Plates were covered and incubated at room temperature (15°C-25°C) by shaking for 1 hour on a microtiter plate shaker. All wells were aspirated and washed 4 times with 300 µL of wash buffer. Immediately, 150 µL of enzyme substrate (3,3’,5,5’ tetramethylbenzidine) was dispensed into all wells and the covered plate was shaken on a microtiter plate for exactly 30 minutes at room temperature (15°C-25°C) before the reaction was stopped with 100 µL of 1M sulfuric acid per well. The optical density was measured at 450 nm by use of an enzyme-linked immunosorbent assay reader (Dynatech Laboratories, Chantilly, Va). The standard curve regression and LTE4 concentrations were calculated after a linear log-logit transformation. The concentration of the sample was determined from tracings were calculated after a linear log-logit transformation.

**STATISTICAL ANALYSIS**

The statistical analysis was performed with use of StatView for Windows statistical software (SAS Institute Inc, Cary, NC). Means and SDs were computed for each of the continuous variables, and differences were compared with 1-way analysis of variance. The significance for categorical variables was computed with use of Pearson χ² test as well as Fisher exact test. P<.05 was considered significant.

**RESULTS**

Montelukast treatment reduced ocular signs (total score, hyperemia, secretion, and chemosis) and symptoms (total score, burning, redness, secretion, tearing, and photophobia) of patients with VKC and asthma. The effect of the drug also persisted 15 days after discontinuation for all symptoms (except tearing) and for 1 sign (hyperemia).

**SUBJECTIVE OUTCOME**

Eight of 10 patients reported an improvement in ocular symptoms after treatment, defined as marked in 6 cases and weak in 2 cases. The improvement persisted at the end of the follow-up period in 6 of 8 patients.

Montelukast treatment significantly decreased 5 of the 7 symptoms evaluated (burning, tearing, photophobia, secretion, and redness), reducing the total symptom score from 13.5±2.1 to 5.0±3.0 (P=.001) (Figures 1, 2, and Table 2). Montelukast reduced the severity of the symptoms, starting from the first days of the treatment (Figure 3). The effect persisted 15 days after discontinuation (total symptom score, 7.5±4.5; P=.007) (Figures 1 and 2).

During the entire period of observation, 3 patients used 1 day of rescue treatment for asthma (inhaled β-agonist), and 2 patients needed 1 day of rescue treatment for eye symptoms (antihistamine eyedrops). Mild adverse effects were reported by 3 patients (transient skin itching during the first days of treatment).

Treatment was also associated with an increase in peak expiratory flow rate in 8 of 10 patients, increasing

![Figure 1. Effects of montelukast sodium treatment on symptoms in patients with vernal keratoconjunctivitis. Limit lines indicate SDs; asterisks, significant differences from baseline (see Table 2).](http://archophthalmol.com/attachment.php?attachmentid=1234567890)
A significant decrease in LTE4 concentration in the urine was observed at the end of monteleukast treatment (baseline, 67.8±56.0 pg/mL; end of treatment, 324.5±522.5 pg/mL; \( P = .03 \)). No significant changes in LTB4 concentration were observed in the urine. The concentrations of LTB4 in the tears and urine were not significantly correlated (\( P = .06; \rho = .591 \)).

**COMMENT**

This pilot study shows that monteleukast, a sulfidopeptide receptor antagonist, when used for asthma treatment, also improves signs and symptoms of a coexisting VKC. Vernal keratoconjunctivitis is a chronic inflammatory disease characterized by frequent exacerbation potentially leading to visual impairment. The signs and symptoms are related to the presence of immune cells infiltrating the conjunctiva and releasing inflammatory mediators, including Lts. It has been demonstrated that Lts are produced in the conjunctiva and are detectable in tear fluid of patients with allergic conjunctivitis, including VKC. In addition, conjunctival administration of LTB4, as well as LTC4 and LTD4, induces vessel dilation, edema, hyperemia, and leukocyte and eosinophil infiltration of the conjunctiva. The biological activities of Lts on the conjunctiva may contribute to the presence of the characteristic symptoms observed in VKC, such as mucous hypersecretion, conjunctival hyperemia, and chemosis.

The effect of monteleukast in reducing burning, photophobia, secretion, and redness persisted 15 days after discontinuation. This carryover effect is in line with previous reports showing a persistence of therapeutic efficacy after discontinuation of monteleukast treatment in patients with asthma and atopic dermatitis.

In this study, we deliberately chose—for ethical reasons—to study the effects of monteleukast in patients with VKC treated with the drug for their coexisting asthma. As in any open clinical study, the results that we obtained could have been influenced by several factors, such as placebo effects and/or improvement of the associated asthma. However, since changes in ocular signs and symptoms were quite marked and consistent in almost all patients, our findings provide the impetus for multicenter, randomized, double-masked, placebo-controlled studies to confirm the potential of this new form of treatment for VKC. It is widely appreciated that symptoms and signs of VKC show a high degree of variability spontaneously or in relation to environmental and allergenic triggering. However, we measured LTB4 in tears as a marker of disease activity and environmental influence. Interestingly, LTB4 release did not decrease in parallel with symptoms, but rather increased 15 days after treatment. This is in line with the report that values of LTB4 are higher during remission than during the acute phase in asthmatic patients.

The decrease in the amount of LTE4 in urine after treatment cannot be easily explained by the mechanism of action of monteleukast, a potent sulfidopeptide receptor antagonist with no reported effect on LT synthesis. Leukotriene E4, a stable product of the rapid enzymatic conversion of LTC4 and LTD4, reflecting their production and turnover during a period of time. Interestingly, a similar reduction of LTC4 was found in nasal

**OPHTHALMOLOGIST EVALUATION**

Ocular signs improved in 7 of the 10 patients. Monteleukast treatment significantly decreased 3 of the 5 signs evaluated (hyperemia, secretion, and chemosis), reducing the total sign score from 7.8±2.1 to 3.5±2.1 (\( P = .002 \)) (Figure 2, Figure 4, and Table 3). The effect persisted 15 days after discontinuation (total sign score, 5.0±1.7; \( P = .03 \)) (Figure 2).

**LT LEVELS IN TEARS AND URINE**

Fifteen days of monteleukast treatment was associated with a significant decrease in LTE4 concentration in the urine of the patients (baseline, 213.4±137.2 pg/mL; end of treatment, 67.8±56.0 pg/mL; \( P = .01 \)).

Figure 2. Effects of montelukast sodium treatment on symptom and sign scores. The treatment significantly decreased both symptom and sign total scores at day 15 (\( P < .001 \) and \( P = .002 \), respectively) as well as 15 days after treatment discontinuation (day 30) (\( P = .007 \) and \( P = .03 \), respectively). Limit lines represent SDs.

<table>
<thead>
<tr>
<th>Table 2. Eye Symptom Scores (Patient Evaluation)</th>
<th>Baseline</th>
<th>After 15 d of Treatment (P)</th>
<th>After 15 d of Treatment Discontinuation (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching</td>
<td>1.67 ± 0.52</td>
<td>0.83 ± 0.75 (.05)</td>
<td>1.83 ± 0.75</td>
</tr>
<tr>
<td>Burning</td>
<td>1.83 ± 0.75</td>
<td>0.33 ± 0.52 (.002)</td>
<td>0.67 ± 0.82 (.01)</td>
</tr>
<tr>
<td>Tearing</td>
<td>1.50 ± 0.55</td>
<td>0.50 ± 0.55 (.02)</td>
<td>1.00 ± 0.89</td>
</tr>
<tr>
<td>Photophobia</td>
<td>2.33 ± 0.52</td>
<td>1.00 ± 1.26 (.02)</td>
<td>0.67 ± 0.82 (.007)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>1.33 ± 0.52</td>
<td>0.67 ± 0.52 (.08)</td>
<td>0.83 ± 0.75</td>
</tr>
<tr>
<td>Secretion</td>
<td>2.33 ± 0.52</td>
<td>0.50 ± 0.55 (.001)</td>
<td>1.17 ± 1.17 (.02)</td>
</tr>
<tr>
<td>Redness</td>
<td>2.50 ± 0.55</td>
<td>1.17 ± 0.41 (&lt;.001)</td>
<td>1.33 ± 0.52 (.001)</td>
</tr>
<tr>
<td>Total score</td>
<td>13.50 ± 4.46</td>
<td>7.50 ± 3.03 (&lt;.001)</td>
<td>7.50 ± 4.46 (.007)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SD.

Figure 4. Mean ± SD total symptom and sign scores for VKC patients treated with montelukast. The effect of montelukast was statistically significant (\( P < .001 \)) after 15 days of treatment and gradually diminished after 30 days of treatment (\( P = .007 \) and \( P = .03 \), respectively). Limit lines represent SDs.

©2003 American Medical Association. All rights reserved.

Downloaded From: http://archophth.jamanetwork.com/pdfaccess.ashx?url=/data/journals/ophth/9906/ on 06/19/2017
washings of children with asthma after treatment with montelukast. This study suggests that montelukast might represent a useful and additional drug in patients with VKC to partially control the disease and to reduce or avoid the risk of corticosteroid treatment. These findings are of some relevance in view of the nature of VKC, ie, an orphan disease and a model of TH2-driven eosinophilic inflammation still waiting for a safe and effective treatment. Our study also suggests the need for multicenter, double-masked, placebo-controlled studies to investigate the potential clinical application of montelukast in the treatment of VKC as well as of other allergic conjunctivitis, such as atopic keratoconjunctivitis and hay fever conjunctivitis with persistent inflammation and late-phase reaction.

Submitted for publication August 6, 2002; final revision received January 3, 2003; accepted January 16, 2003.

This study was supported by an unrestricted grant from Merck & Co Inc, Whitehouse Station, NJ (Medical School Grant Scheme).

Corresponding author and reprints: Sergio Bonini, MD, Institute of Neurobiology and Molecular Medicine, National Research Council, Via C. Marx, 15/4300137 Roma, Italy (e-mail: se.bonini-CNR@flashnet.it).

Table 3. Eye Sign Scores (Ophthalmologist Evaluation) in Patients With Vernal Keratoconjunctivitis Treated With Montelukast

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After 15 d of Treatment (P)</th>
<th>After 15 d of Treatment Discontinuation (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarsal papillae</td>
<td>1.83 ± 0.75</td>
<td>1.50 ± 1.22</td>
<td>1.50 ± 1.05</td>
</tr>
<tr>
<td>Bulbar papillae</td>
<td>0.50 ± 0.84</td>
<td>0.17 ± 0.41</td>
<td>0.50 ± 0.55</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>2.17 ± 0.75</td>
<td>0.83 ± 0.41 (.003)</td>
<td>1.17 ± 0.75 (.02)</td>
</tr>
<tr>
<td>Secretion</td>
<td>1.83 ± 0.75</td>
<td>0.50 ± 0.84 (.005)</td>
<td>1.17 ± 0.41</td>
</tr>
<tr>
<td>Chemosis</td>
<td>1.50 ± 1.05</td>
<td>0.50 ± 0.55 (.35)</td>
<td>0.67 ± 0.32</td>
</tr>
<tr>
<td>Total score</td>
<td>7.83 ± 2.14</td>
<td>3.50 ± 2.07 (.002)</td>
<td>5.00 ± 1.67 (.03)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SD.

REFERENCES
