Efficacy of Tremacamra, a Soluble Intercellular Adhesion Molecule 1, for Experimental Rhinovirus Infection

A Randomized Clinical Trial

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The common cold is a ubiquitous illness of humans that is associated with significant complications, especially otitis media, sinusitis, and exacerbations of asthma. Rhinoviruses are the most frequent causes of the common cold. Efforts to prevent or treat colds by interfering with rhinovirus infection generally have been unsuccessful. Antiviral agents that are nontoxic and effective have not yet been developed and traditional vaccine approaches to prevention are not feasible due to the large number of distinct rhinovirus serotypes.

In 1984, Abraham and Colonno demonstrated that the attachment of the majority of rhinovirus serotypes to cells was dependent on a single cellular receptor that was subsequently identified as intercellular adhesion molecule 1 (ICAM-1). These observations presented the possibility of receptor blockade as a method for the prevention of rhinovirus infection. An attempt to prevent experimental rhinovirus infection in humans with a recombinant soluble ICAM-1 (tremacamra, formerly BIRR 4) has shown possible efficacy in early studies.

Context Attachment of most rhinovirus subtypes to cells depends on a cellular receptor, the intercellular adhesion molecule 1 (ICAM-1). A recombinant soluble ICAM-1 (tremacamra, formerly BIRR 4) has shown possible efficacy in early studies.

Objective To determine the efficacy and safety of intranasal administration of tremacamra in experimental rhinovirus colds in humans.

Design Four randomized, double-blind, placebo-controlled trials conducted in January to March 1996.

Setting and Subjects Volunteers between the ages of 18 and 60 years who had an antibody titer of 1:4 or less to the challenge virus. Subjects were isolated in a hotel room during study days 0 to 8; symptoms were recorded through day 14. A total of 198 subjects were randomized, of whom 196 received drug or placebo and were included in the safety analysis. A total of 177 subjects were included in the efficacy analysis.

Interventions Tremacamra or placebo was given beginning 7 hours before inoculation with rhinovirus type 39 (preinoculation studies) or 12 hours after (postinoculation studies). Tremacamra as an inhaled solution or as a powder (each given preinoculation and postinoculation for a total of 4 studies) and placebo were given in 6 doses at 3-hour intervals daily during days 1 through 7. Recipients of active treatment received 367 µg of tremacamra per nostril per dose for a total of 4.4 mg/d.

Main Outcome Measures Effect of tremacamra on infection, as determined by virus isolation and seroconversion, and on illness, as determined by symptom scores, antibody titer of 1:4 or less to the challenge virus. Subjects were isolated in a hotel room during study days 0 to 8; symptoms were recorded through day 14. A total of 198 subjects were randomized, of whom 196 received drug or placebo and were included in the safety analysis. A total of 177 subjects were included in the efficacy analysis.

Results A total of 88 (92%) of the 96 subjects in the placebo groups and 69 (85%) of the 81 subjects in the active treatment groups were infected (P = .19). For placebo vs tremacamra, respectively, the total symptom score (± 95% confidence interval [CI]) was 17.6 (± 2.7) vs 9.6 (± 2.9), the proportion of clinical colds was 64/96 (67% ± 9%) vs 36/81 (44% ± 11%), and the nasal mucus weight was 32.9 (± 8.8) g vs 14.5 (± 9.4) g (P < .001 for all comparisons). Tremacamra was not associated with adverse effects or evidence of absorption through the nasal mucosa and did not interfere with development of neutralizing antibody.

Conclusion Tremacamra reduced the severity of experimental rhinovirus colds. Whether tremacamra will be useful clinically will require further study.

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man subjects with a monoclonal antibody to the cellular ICAM-1 had limited success.4 More recently, a recombinant soluble ICAM-1 (tremacamra, formerly BIRR 4, prepared by Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Conn) consisting of the extracellular portion of the ICAM-1 has been found to be effective for inhibition of rhinovirus replication in cell culture monolayers and explants of human respiratory epithelium.5,6 Recent studies have suggested that the host inflammatory response, particularly interleukin 8 (IL-8), may play a role in the pathogenesis of common cold symptoms following rhinovirus infection.7-11 We conducted 4 randomized controlled trials to determine the effect of intranasal administration of tremacamra on infection, IL-8 response, and illness in experimental rhinovirus colds. The 4 studies evaluated 2 formulations of tremacamra taken by subjects before or after rhinovirus inoculation.

METHODS

Subjects
Subjects were recruited for these studies from university communities at the University of Virginia, Charlottesville, and the Medical University of South Carolina, Charleston. Subjects were required to be in good health, nonsmokers, and between the ages of 18 and 60 years. In addition, subjects were required to be susceptible to the study virus as evidenced by a serum neutralizing antibody titer of 1:4 or less to the virus. Subjects were excluded if they had a history of allergic disease or nonallergic rhinitis, abnormal nasal anatomy or mucosa, or a respiratory tract infection in the previous 2 weeks. Pregnant or lactating women or women not taking medically approved birth control were also excluded. Written informed consent was obtained prior to study participation in a form approved by the institutional review board of each study institution and subjects were compensated for participation.

Study Medication
The active treatment in this study was tremacamra, a recombinant, soluble form of the membrane-bound ICAM-1 glycoprotein. Two different formulations of tremacamra were evaluated: a phosphate-buffered saline nasal spray solution and a carboxymethylcellulose (CMC)–mannitol-based powder formulation. In each study, the placebo consisted of inactive ingredients and was identical in appearance to the active preparation. In addition, for the powder formulation studies, a second control consisting of mannitol powder without the CMC was studied. All study medications were administered by study staff as 6 doses each day at 3-hour intervals for 7 days. Subjects were randomly assigned to receive either tremacamra or matching placebo at the time of enrollment into each study using blinded computer-generated sequences (ClinPro/LBL version 5.0, Clinical Systems Inc, Garden City, NJ). The supervisor of clinical trials support and manager of clinical drug safety for Boehringer Ingelheim Pharmaceuticals Inc maintained secure copies of the treatment codes and ensured that all clinical trial personnel, subjects, and employees of the sponsor remained blinded until all data were collected for all 4 studies.

The solution formulation was administered using a medication bottle equipped with a Pfeiffer (Ing. Erich Pfeiffer GmbH, Randolfzell, Germany) metered nasal spray pump. The pump delivered 70 µL of solution containing 183 µg of tremacamra with each spray. The medication was administered as 2 sprays per nostril, 6 times daily for a total daily dose of 4.4 mg. The powder formulation was provided in gelatin capsules each containing 367 µg of tremacamra. The contents of the capsule were administered using a dry powder inhalation device equipped with a nasal adapter. One capsule was administered to each nostril 6 times each day for a total daily dose of 4.4 mg.

Challenge Virus
The challenge virus used for this study was rhinovirus type 39 (supplied by Jack M. Gwaltney, Jr, MD, University of Virginia, Charlottesville). Rhinovirus type 39 is a major group rhinovirus that requires ICAM-1 for attachment to cells. The median effective dose of tremacamra for rhinovirus type 39 is less than 1 µg/mL in both human embryonic lung fibroblasts and HeLa cells and in human adenoid explants.12 The challenge pool used for this study had been safety tested according to consensus guidelines.12 All subjects were inoculated with a total of 100 to 300 median tissue culture infective dose (TCID50). The virus was administered as drops in 2 inocula of 250 µL per nostril given approximately 15 minutes apart while the subjects were supine.

Study Design
A series of 4 randomized rhinovirus challenge studies were performed. The solution and powder formulations of tremacamra were each evaluated in preinoculation and postinoculation studies. At the University of Virginia, the study medications were initiated 7 hours prior to viral challenge (preinoculation). At the Medical University of South Carolina, the study medication was begun 12 hours after virus challenge (postinoculation). Both formulations of tremacamra were evaluated at each site. In the preinoculation studies, the virus challenge was administered 1 hour after the third dose of tremacamra and the 3 remaining doses of study medication were then given as scheduled. In the postinoculation studies, the virus challenge was administered in the evening of study day 0 approximately 12 hours prior to the first dose of study medication on the morning of study day 1. Except as noted, all subjects received 6 doses of study medication on study days 1 through 7. At each study site, the study of the solution formulation was planned for 18 subjects who would receive the active treatment and 18 subjects who would receive placebo. The study of the powder formulation at each site was planned for 27 subjects who would receive active treatment, 18 who would receive a placebo of CMC-mannitol, and 18 who would receive mannitol alone.
Subjects were isolated in individual hotel rooms from study day 0 (the day of virus challenge) to study day 8. On each of these days a symptom score and nasal lavage for virus isolation were done in the morning prior to the first dose of medication and a second symptom score was done each evening. On study day 8, subjects were released from isolation but continued to record symptom scores each evening through day 14. The subjects returned to the study site and were given a final dose of study medication on study day 21. A final serum sample for detection of anti-tremacamra antibodies was collected on study day 42.

**Viral Isolation**

Virus shedding was detected by virus isolation in cell culture. Nasal wash specimens were collected by instillation of 5 mL of 0.9% saline into each nostril. This wash was then expelled into a waxed paper cup and kept chilled for 1 to 2 hours until it was processed for viral cultures. Tremacamra was removed from the specimens by treatment with anti–ICAM-1 antibody adsorbed to an agarose support (Affi-Gel 10, Bio-Rad Laboratories, Hercules, Calif). Each specimen was inoculated into 2 tubes of human embryonic lung fibroblast cells (either MRC-5 or WI-38) and incubated on roller drums at 33°C for 14 days. At the University of Virginia, 2 tubes of HeLa-I cells, a HeLa cell line enriched for the production of ICAM-1, were also inoculated for each specimen. Rhinovirus was identified by the development of typical cytopathic effect. Subjects with a positive viral culture on any of the postchallenge study days were considered infected. Viral titers in the original nasal wash specimens were determined from specimens stored at –80°C by removal of the trelicamra as described above and then culturing serial 10-fold dilutions in microtiter plates of MRC-5 cells. For calculation of the mean virus titers, specimens that were positive on initial isolation but negative on reisolation for quantitative culture were defined as containing 10⁻¹⁻² TCID₅₀ per milliliter or 10⁻¹⁻² TCID₅₀ per milliliter depending on whether the initial isolate was detected in 1 or both cell culture tubes, and cultures that were negative on initial isolation were defined as containing 10⁻⁰⁻² TCID₅₀ per milliliter.

**Viral Serology**

Antibody to the challenge virus was detected by serum neutralizing titers done using standard methods. Serum specimens for antibody testing were collected during screening, immediately prior to virus challenge (acute), and again 21 days later (convalescent). Subjects with at least a 4-fold rise in antibody titer to the challenge virus when the convalescent serum sample was compared with the acute serum sample were considered infected.

**Evaluation of Illness Severity**

Illness severity was assessed by a modification of a previously published method. Symptom scores were recorded prior to virus challenge (baseline) and twice each day at approximately 12-hour intervals for the next 8 days. On study days 9 through 14 each subject recorded his/her symptom score once per day in the evening. At each evaluation, subjects were asked to judge the maximum severity of the following 8 symptoms in the interval since the last symptom evaluation: sneezing, rhinorrhea, nasal obstruction, sore throat, cough, headache, malaise, and chilliness. Each symptom was assigned a severity score of 0 to 3 corresponding to a report of symptom severity of absent, mild, moderate, or severe. If symptoms were present at baseline, the baseline symptom score was subtracted from the reported symptom score. Fourteen subjects (8%) had a baseline total symptom score of more than 0 (if symptoms for these subjects improved, their score was 0). Twelve subjects had a baseline symptom score of 1 and baseline scores of 2 and 3 were reported by 1 subject each. The highest of the 2 daily evaluations was taken as the daily symptom score for each symptom. The daily symptom scores for the 8 individual symptoms were summed to yield the total daily symptom score. The total daily symptom scores for the first 5 days after virus challenge (study days 1-5) were summed and on the evening of study day 5, all subjects were asked “Do you feel you have had a cold?” Subjects who had a total symptom score of at least 6 and either at least 3 days of rhinorrhea or the subjective impression that they had a cold were defined as having a clinical cold.

The weight of expelled nasal secretions was determined by providing all subjects with packets of preweighed nasal tissues. After the tissues were used they were stored in an air-tight plastic bag. Each morning the used tissues, together with any unused tissues from the original packet, were collected and weighed. Values reported are the cumulative nasal mucus weights for days 1 through 7 after virus challenge.

**The IL-8 Assay**

Concentrations of IL-8 in nasal lavage were determined with a commercially available enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minn) as previously described.

**Safety Evaluations**

In addition to routine adverse event recording, the safety of tremacamra was assessed in 3 ways. A visual examination of the nasal mucosa was done by the investigators prior to viral challenge and following treatment on study days 1 and 7. Serum samples for the measurement of immunoreactive soluble ICAM-1 were collected prior to administration of tremacamra and 1 hour after the fifth dose on study days 1, 3, and 7. Additional serum specimens for measurement of antibody to tremacamra were collected prior to treatment and on study days 7 and 21. Subjects were given a dose of tremacamra on study day 21 and a final measurement of serum antibody to tremacamra was done on serum samples collected on study day 42.

Immunoreactive ICAM-1 in serum samples was measured by ELISA. The assay detected both tremacamra and
natural circulating ICAM-1. The precision of the assay was determined with pools of human serum samples containing known concentrations of circulating ICAM-1 that were spiked with tremacamra so that the total immunoreactive ICAM-1 ranged from approximately 100 to 1000 ng/mL. Intra-assay variability ranged from 0.8% to 17.3% and interassay variability ranged from 4.1% to 19.9%. The lower limit of quantitation was 80 ng/mL.

Human antibody to tremacamra was assayed with an ELISA method that used tremacamra adsorbed to microwell plates. A variability factor was calculated for each study based on a comparison of the pretreatment and posttreatment samples from the placebo subjects. The variability factor ranged from 16% to 40% for the 4 studies. Posttreatment samples from subjects treated with tremacamra were considered positive if they differed from the pretreatment sample by 2 SDs and the difference was greater than the variability factor defined for the study. As a positive control, samples from nonhuman primates challenged with tremacamra were analyzed in parallel and yielded antibody responses that were at least 10-fold greater than the limit of detection for this assay.

Statistical Analysis

The sample size for these studies was based on previous studies using the rhinovirus challenge model. The sample size in each of the 4 studies as planned was adequate to detect a reduction in the incidence of clinical colds from 75% in the placebo groups to 25% in the active treatment groups at 1-sided levels of \( \alpha = .05 \) and \( 1-\beta = .80 \). In addition, the sample size was adequate to detect a change in the total symptom score of 5 units assuming an SD of 5.8 units. Randomization in the powder formulation was based on a ratio 3:2:2 (active to CMC-mannitol control to mannitol control) and was designed to provide adequate sample size for comparison of the active with each placebo group while minimizing the number of subjects required for the study. All comparisons reported are based on 2-sided alternatives with an \( \alpha \) of .05 or less considered statistically significant.

Continuous variables (symptom scores and nasal mucus weights) were analyzed on an individual trial basis using simple t tests and pooled over all trials using an analysis of variance with terms for treatment, study, and treatment-by-study interaction. For the safety analysis, within-subject changes in the serum levels of immunoreactive ICAM-1 (postdose minus predose) were analyzed using the analysis of variance model with study and treatment-by-study interaction.

Proportions were analyzed using the Fisher exact test for the individual studies and the Mantel-Haenszel statistic stratified on study for the combined analysis. A posthoc analysis of IL-8 concentrations and viral titer in nasal wash was done on the specimens collected during the postinoculation studies. These data were compared using the Mann-Whitney test. All statistical analyses were performed using SAS software version 6.12 (SAS Institute Inc, Cary, NC).

The individual components of this trial were conducted as 4 separate studies; however, the studies were planned simultaneously and were identical in all aspects with the exception of timing of study drug initiation and the study drug formulation. No interim analyses or unblinding occurred prior to the completion of all 4 phases of the trial. Treatment-by-study interaction was not significant in any of the analyses so the results of the 4 studies were pooled. In addition, the results are presented separately to demonstrate the consistency of the results prior to pooling.

RESULTS

The demographics were similar in the treatment groups. The mean (SD) age of the subjects was 27 (9) years and 53% were men. The racial distribution was 79% white, 15% black, and 6% of Asian descent. A total of 198 were randomized, of whom 196 received study medication (FIGURE 1). Two subjects who were enrolled but did not receive study medication and were not challenged with the study virus were excluded from both the efficacy and the safety analysis. Nine subjects in the tremacamra groups and 10 in the placebo groups who received study medication were excluded from the efficacy analysis but were included in the safety analysis. Seventeen of those subjects were excluded after they were found to have serum neutralizing antibody titers ratio of more than 1.4 to the study virus prior to challenge. These subjects were eligible for randomization (antibody titer \( \geq 1.4 \)) based on screening antibody titers done 1 to 3 months prior to virus challenge but, in assays performed after the completion of the study, were found to have elevated antibody titers in serum samples collected on the day of virus challenge. These subjects as a group had reduced cold symptoms compared with those subjects who had antibody titers of 1.4 or less at the time of virus challenge. Two additional subjects developed illnesses (gastroenteritis and streptococcal pharyngitis) unrelated to the challenge virus and were excluded from the efficacy analysis. None of the overall statistical conclusions reported in this article are changed if these 19 subjects are included in the efficacy analysis.

Effect of Tremacamra on Rhinovirus Infection and Illness

Of the 177 subjects included in the efficacy analysis, 81 received tremacamra and 96 received placebo (TABLE). Eighty-eight (92%) of the placebo-treated subjects and 69 (85%) of the tremacamra-treated subjects were infected (by either virus isolation or serologic conversion) with the challenge virus (\( P = .19 \)). Virus shedding was detected in 88 (92%) of the 96 placebo-treated subjects and in 63 (78%) of the 81 tremacamra-treated subjects (\( P = .009 \)). A significant increase in antibody titer was found in 49 (52%) of the 96 placebo-treated subjects and in 44 (54%) of the 81 tremacamra-treated subjects, respectively.

Tremacamra had a significant impact on all measures of illness (Table).
The total symptom score (study days 1-5) was reduced by 45%, the proportion of subjects with clinical colds was reduced by 23%, and the total nasal mucus weight was reduced by 56%. The mean daily symptom score was significantly lower in the tremacramra-treated subjects on each of the study days, 1 through 7 (Figure 2). The reduction in symptom score was a result of a consistent reduction in all of the symptoms assessed during the study. Statistically significant reductions were seen in cumulative score for study days 1 through 5 for all symptoms except chilliness (Figure 3).

**Effect of Tremacramra on Nasal Lavage Virus Titer and IL-8 Concentration**

The effect of tremacramra on the concentration of virus and IL-8 in nasal lavage fluid was assessed for the subset of patients in the postinoculation treatment studies. The geometric mean titer of virus present in the lavage fluid was significantly reduced by active treatment on study days 2, 3, and 4 (Figure 4). Similarly, the infected subjects in the active treatment groups had significantly lower IL-8 concentrations on study days 2, 3, and 4 than infected subjects in the placebo groups (Figure 5).

**Safety and Tolerability**

All subjects who received treatment were included in the analysis of the safety and tolerability of tremacramra. Overall, tremacramra was well tolerated. Thirty-seven (41%) of the 90 subjects who received tremacramra and 53 (50%) of the 106 subjects who received placebo reported 1 or more adverse events. The most common adverse events reported were headache (reported by 15 [17%] and 17 [16%] of the tremacramra-treated and placebo-treated subjects, respectively) and nasal irritation. The headaches ranged in severity from mild to severe with duration no longer than 2 days. No patients discontinued medication usage due to headache. The nasal irritation appeared to be associated with the CMC.
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Table. Effect of Tremacamra on Rhinovirus Infection and Illness

<table>
<thead>
<tr>
<th>Study Type</th>
<th>No. of Subjects</th>
<th>Total Symptom Score, Mean (95% Confidence Interval)</th>
<th>P Value</th>
<th>No. of Clinical Colds, % (±95% Confidence Interval)</th>
<th>P Value</th>
<th>Weight of Nasal Mucus, g, Mean (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinoculation Solution</td>
<td>Tremacamra 17</td>
<td>Placebo 17</td>
<td>9.1 (4.2)</td>
<td>13.3 (4.9)</td>
<td>&gt;0.05</td>
<td>9 (53 ± 24)</td>
<td>11 (65 ± 23)</td>
</tr>
<tr>
<td>Postinoculation Solution</td>
<td>Powder 20</td>
<td>27†</td>
<td>12.8 (6.1)</td>
<td>20.3 (6.5)</td>
<td>&gt;0.05</td>
<td>9 (45 ± 22)</td>
<td>20 (74 ± 17)</td>
</tr>
<tr>
<td>Combined†‡</td>
<td>81</td>
<td>96</td>
<td>9.6 (2.9)</td>
<td>17.6 (2.7)</td>
<td>&lt;0.001</td>
<td>4 (24 ± 20)</td>
<td>11 (61 ± 23)</td>
</tr>
</tbody>
</table>

*Preinoculation refers to those studies in which drug was given before virus; postinoculation, drug was given after virus.
†Includes all placebo-treated subjects. Mean total symptom score (95% confidence interval) for the carboxymethylcellulose and mannitol placebos were 21.1 (8.4) and 20.3 (6.3), respectively, in the preinoculation studies and 23.6 (7.3) and 16.0 (8.2) in the postinoculation studies.
‡Means for the combined results are adjusted for study and treatment-by-study interaction using the analysis of variance model. Confidence intervals for combined proportions are based on simple binomial proportions. P values for combined proportions are calculated based on Mantel-Haenszel odds ratios stratified by study.

Figure 2. Mean Total Daily Symptom Scores in Tremacamra and Placebo-Treated Subjects

The vertical line indicates the end of the tremacamra treatment period. The difference in mean total daily symptom score is statistically significant (analysis of variance, P<.05) on each of the study days 1 to 7 after inoculation.

additive in the powder formulation. Thirteen (24%) of the 54 subjects who received the tremacamra powder formulation and 10 (28%) of the 36 subjects who received the matching (CMC containing) placebo reported nasal irritation. In contrast, 1 (3%) of the 34 subjects who received the mannitol powder placebo reported nasal irritation (P<.01 for comparison of mannitol placebo with CMC placebo). Nasal irritation was reported by 3 (8%) of the 36 subjects in both the tremacamra and placebo solution groups.

Other evaluations of safety revealed no evidence of toxic effects or unwanted effects associated with the administration of tremacamra. Of the 89 subjects treated with tremacamra who were available for evaluation on day 7 of the study, 4 (4%) had abnormal nasal color and 1 (1%) had moderate or severe mucosal edema. Of the 105 placebo-treated subjects, 4 (4%) had abnormal nasal color and 1 (1%) had moderate or severe mucosal edema.

There was no evidence that tremacamra was absorbed across the nasal mucosa. Mean (±95% confidence interval) for the predose serum levels of immunoreactive ICAM-1 were 219 (±16) ng/mL and 213 (±12) ng/mL in the tremacamra and placebo-treated subjects, respectively. The change in ICAM-1 concentration from this baseline was −6 (±4), −2 (±4), and 3 (±6) ng/mL for the tremacamra-treated subjects and −8 (±4), 1 (±4), and 5 (±6) ng/mL for the placebo-treated subjects on study days 1, 3, and 7, respectively.

Three (3%) of the 90 subjects who were treated with tremacamra had positive ELISA results for human antibody to tremacamra in a single specimen, 2 subjects on day 7, and 1 subject on day 21. Each of these subjects had subsequent serum samples that were negative in this assay suggesting that the positive results did not represent a true antibody response to tremacamra.

**COMMENT**

These are the first human trials to test the effectiveness of receptor blockade with soluble ICAM-1 in rhinovirus infections. The feasibility of receptor blockade was first suggested by the observation that many different rhinovirus serotypes share the same cellular receptor. This receptor was subsequently identified as ICAM-1. In early studies of the antiviral potential of ICAM-1, soluble ICAM-1, a truncated form of ICAM-1 in which the transmembrane domain of the protein have been deleted, was shown to prevent infection with rhinovirus in vivo. Later studies confirmed that soluble ICAM-1 was effective against a broad spectrum of rhinovirus serotypes in a variety of different cell lines. The median effective dose for most of the 89 serotypes of virus that bind to the ICAM-1 receptor was found to be 10 µg/mL or less.

There have been 2 previous studies of ICAM-1 receptor blockade for prevention of rhinovirus infection in vivo. Soluble ICAM-1 prevented infection with rhinovirus type 16 in chimpanzees treated with 10 mg of soluble ICAM-1 administered intranasally 0 to 10 minutes after rhinovirus challenge. A different approach to receptor blockade, prophylaxis with intranasal monoclonal antibody to ICAM-1, was attempted by Hayden et al in volunteers with experimental colds. In the most successful of these studies, a total of 1 mg per subject of anti–ICAM-1 antibody was given over a period beginning 3 hours before and ending 36 hours after virus challenge. This treatment regimen reduced symptoms and viral shedding during the time the medication was being administered; however, when the medication was dis-
continued the amount of virus shedding increased and symptoms became more severe. Both of these previous studies suggested the potential effectiveness of receptor blockade.

The effect of tremacamra on the symptoms of rhinovirus colds compares favorably with other common cold therapies. Although a number of antiviral compounds have had activity against rhinovirus infection in vitro, the in vivo efficacy of antiviral agents generally has been disappointing. PI-32 Pirodavir and interferon alfa are effective when given as prophylaxis but have no effect on established infection.26-33 Currently available symptomatic therapies are variably effective; however, none of these agents has activity against a broad spectrum of common cold symptoms.

This study was designed to test the effect of tremacamra on rhinovirus infection when the medication was given either before (preinoculation) or after (postinoculation) allowing the viral infection to be established. A previous study in volunteers challenged with rhinovirus type 39 found that most subjects have evidence for 1 cycle of virus replication by 12 hours after virus challenge.34 The efficacy of tremacamra on rhinovirus-induced illness was similar when the medication was given either 7 hours prior to virus challenge or 12 hours after challenge (but before onset of symptoms). Thus, even when given after viral replication was established, tremacamra reduced the amount of virus produced and had a beneficial effect on symptoms. The lack of difference in the outcome between the preinoculation and postinoculation treatment groups suggests that the observed effects were not simply due to prevention of the initial viral infection but rather to sustained antiviral effects. It remains to be determined whether treatment with soluble ICAM-1 after the onset of symptoms will have a beneficial effect on viral replication and illness.

Recent investigations of the pathogenesis of rhinovirus infection have suggested a role for inflammatory mediators in the production of common cold symptoms and the lower respiratory complications of this illness.10 In untreated subjects there is a direct correlation between the concentration of inflammatory mediators in nasal secretions and the severity of common cold symptoms. Treatment 12 hours after virus challenge with tremacamra was associated with a significant decrease in the elaboration of IL-8. This observation suggests that ongoing viral replication contributes to the intensity of the inflammatory response and this response can be moderated by antiviral agents.

One barrier to the practical use of soluble ICAM-1 for prevention or treat-
ment of colds is clearance of the medication from the nasal cavity by the mucociliary defenses of the nasal mucosa. Two different formulations of the medication were used in this study in an attempt to assess the effects of formulation on drug effectiveness. The CMC in the powder formulation was intended to retard clearance of the active drug from the nasal cavity. There was no apparent difference in the efficacy of the 2 formulations. The CMC component of the powder formulation was associated with nasal irritation.

In summary, tremacamra, a recombinant soluble ICAM-1 molecule, was effective in reducing the symptoms of experimental common colds. This reduction in symptoms was apparent regardless of whether the drug was given before or after the challenge with the virus. This study demonstrates the feasibility of receptor blockade as prophylaxis of common cold symptoms. The effect of this drug on symptom severity when given after symptoms have begun or on the complications associated with the common cold remains to be determined.

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