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Continuous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy

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Key words: adhesion molecules; allergic inflammation; antihistamines; long-term treatment; mite allergy.

Background: Allergic reaction is characterized by a complex inflammatory process. Some of the new antihistamines have antiallergic effects and can affect the inflammatory cell recruitment via adhesion molecule downregulation. We aimed to assess in a 12-month study whether continuous treatment with an antihistamine (terfenadine) can reduce respiratory symptoms and local inflammation in children with mite allergy.

Methods: The study was double-blind and placebo-controlled: it involved two parallel groups of children suffering from rhinoconjunctivitis and/or mild intermittent asthma due to mite allergy. They received either terfenadine (1 mg/kg per body weight per day) or placebo for 1 year. Nasal, conjunctival, and bronchial symptoms were recorded by diary cards; at each of the programmed control visits, a nasal scraping for inflammatory cells and ICAM-1 was performed. Some additional clinical parameters were also recorded: days of school absence, extra visits for acute respiratory symptoms, and days of hospital admission.

Results: Only children treated with terfenadine achieved significant control of symptoms ($P < 0.05$ in 8 out of 12 months) and allergic inflammation, as shown by inflammatory cell infiltrate and ICAM-1 expression at nasal level ($P < 0.001$), and had significantly fewer extra visits and school absences than the placebo group ($P < 0.03$). No side-effects were reported in either group.

Conclusions: The present study demonstrates that continuous terfenadine treatment (1 mg/kg body weight per day) could decrease respiratory symptoms and allergic inflammation, and it had an additional antiallergic effect in reducing ICAM-1 expression on nasal epithelial cells. Therefore, the present results confirm the efficacy of a long-term therapeutic strategy in controlling allergic inflammation.

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Table 1. Evaluated parameters

• Baseline demographic (enrollment)
– Age, height
– Respiratory function
– Der p 1, Der f 1, Fel d 1 in home
• Clinical diary card (whole study period)
– Symptoms/drug intake
– Omitted doses
– Days of school absence
– Hospitalization
• Control visits (0, 4, 8, 12 months)
– Symptom score
– Rhinocytometry (neutrophils, eosinophils, ICAM-1)
– Respiratory function
• Extra visits (when needed)
– Clinical evaluation
– Nasal scraping for cytometry

During the last 15 years, the pathophysiologic interpretation of the allergic reaction has changed dramatically, and a complex interactive network of inflammatory cells and soluble mediators has been discovered. We can now speak of allergic inflammation, since it is well known that an infiltrate of inflammatory cells invariably occurs in the target organs after allergen-driven mast-cell activation (1–3). The cell adhesion molecule (CAM) system is deeply involved in cellular infiltration (4, 5).

Both the nasal and conjunctival epithelia are easy to study since specimens can be collected with minimal discomfort for the patient, and the inflammatory events can be investigated either during the natural exposure to the allergen or by allergen-specific challenge. By means of these models, the following important facts have been discovered:

- 1) the ICAM-1 molecule is promptly expressed on nasal and conjunctival epithelial cells in response to specific challenge and under natural exposure to the allergen (6, 7)
- 2) the expression of the ICAM-1 molecule correlates closely with inflammatory cell (neutrophils and eosinophils) infiltration
- 3) mite-allergic patients show weak expression of ICAM-1 and weak cellular infiltration also when they are completely symptom-free.

The third phenomenon is termed minimal persistent inflammation (MPI) (8). This phenomenon may be of relevance, since ICAM-1 is a specific receptor for human rhinoviruses (9).

It is well known that some of the new antihistamines can, like the H₁ antagonists, modulate the allergic inflammation. On these premises, we have previously demonstrated that continuous treatments are more effective than on-demand ones (10, 11) in controlling both symptoms and inflammatory events in allergic subjects. Furthermore, everyday clinical practice showed that children receiving continuous

Table 2. Demographic data of patients at enrollment

	Active	Placebo	P value (t-test)
n	10	10	
M/F	8/2	7/3	NS
Age (years) mean (SD)	8.5 (3)	7.9 (2.7)	NS
Height (cm) mean (SD)	127 (16)	123 (19)	NS
Asthma	8/10	7/10	NS
Der p 1 (µg/g dust)			
Baseline	0.41 (0.3)	0.31 (0.3)	NS
End	0.53 (0.4)	0.38 (0.3)	NS
Der f 1 (µg/g dust)			
Baseline	2.82 (4.2)	2.41 (2.5)	NS
End	3.90 (3.5)	3.12 (3.2)	NS
Fel d 1 (µg/g dust)			
Baseline	17.1 (16)	15.3 (10)	NS
End	12.3 (13)	18.1 (11.1)	NS

and prolonged antihistamine treatment usually have fewer respiratory symptoms and generally benefit clinically (12, 13). In the present pilot study, we aimed to test this observation, using a double-blind, placebo-controlled design. In other words, we investigated whether long-term continuous treatment in children with mite allergy could reduce both the allergic inflammation and the morbidity of upper respiratory infections by monitoring several clinical parameters.

Material and methods

Study design

The study was randomized, double-blind, placebo-controlled: it involved two parallel groups of 10 patients, receiving daily either terfenadine or placebo for 12 months (December 1995–December 1996). The concentration of perennial allergens in dust samples from the patients' homes was assessed at the enrollment and at the end of the study. Several clinical parameters were monitored during the trial, as detailed below. A clinical diary card of symptoms and drug intake was recorded during the whole study. At each of the four control visits, we assessed the clinical condition; a nasal scraping (for inflammatory cells and ICAM-1 expression) was performed, and a blood sample was obtained for ICAM-1 and eosinophil cationic protein (ECP) serum levels. Days of school absence and hospital admission were recorded as well. Extra visits (in addition to

the programmed ones) were allowed in case of acute respiratory symptoms; in such cases, nasal scraping was performed. Compliance with the treatment was assessed by counting the unused doses of the drug. The study was approved by the ethical committee of the Department of Internal Medicine (Genoa University, Italy). All the children's parents gave their informed consent. The evaluated parameters are summarized in Table 1.

Patients

Twenty patients (15 boys and five girls), aged 4–13 years (8.2 ± 2.8 years), were selected from an outcoming population, and enrolled in the study. All patients showed single sensitization to house-dust mite, assessed by skin testing (wheal >3 mm, +++ or more) and RAST (class III or higher). All patients suffered from rhinoconjunctivitis and some of them also from mild intermittent asthma (Table 2). None of them suffered from anatomic alterations of the upper airways, immunologic deficiencies, or major systemic diseases (diabetes, anemia, cystic fibrosis, inherited metabolic disorders). No child had a history of cardiac disease and/or arrhythmias.

The patients were observing proper environmental precautions at their enrollment; nevertheless, the concentration of Der p 1, Der f 1, and Fel d 1 was measured (Laboratory ALK-Abelló, Milan, Italy) in the dust from the patients' homes at the beginning and at the end of the study, as a complementary index of the homogeneity of the groups.

Diary card and clinical evaluation

The patients' parents were asked to record daily on a proper card the presence and severity of respiratory symptoms. Nasal symptoms (itching, sneezing, obstruction, rhinorrhea), eye symptoms (conjunctival itching, lacrimation, conjunctival hyperemia), and respiratory symptoms (cough intensity and frequency, and dyspnea) were considered. Each of these groups was graded on an arbitrary four-point scale: 0=absent, 1=mild, 2=moderate, 3=severe, as previously described (9). The diary card also included the number of daily doses of concomitant treatment assumed, as reported below (one point for each dose of each drug). Some additional parameters were also recorded: number of extra visits for respiratory symptoms, days of school absence, and days of hospital admission.

Investigational drug and concomitant treatments

The investigational drug (terfenadine) at half the recommended dose (i.e., 1 mg/kg per body weight per day) was prepared as syrup and administered daily in the evening during the whole study period. The placebo treatment of the matched group was indistinguishable in flavor and taste from the active one. The number of omitted doses during the study was recorded on the diary card.

All patients were allowed to take the usually prescribed drugs when needed. These drugs included inhaled albuterol (100 µg/puff: 1–2 puffs on demand), inhaled cromolyn (20 mg t.i.d.), nasal and inhaled corticosteroids (beclomethasone 50 or 200 µg, respectively, b.i.d.), and short courses of systemic corticosteroids (prednisone 1 mg/kg body weight per 3 days). Furthermore, any other concomitant medication prescribed by the pediatrician or by the allergist (including antibiotics, mucolytics, and theophylline) was carefully recorded on the diary card. Only macrolides and azolic antifungals were excluded for safety reasons.

Cytologic assessment

Nasal scrapings were performed as previously reported (3, 4). Briefly, a cotton tip (Minitip Colturette, Beckton-Dickinson) was used in both nostrils after nasal lavage with Ringer's solution (10 ml). Specimens obtained from the middle third of the inferior turbinate were placed in PBS solution (2 ml) to allow cell elution. The suspension was filtered and cytopun, and slides were prepared. Specimens were immediately spread on glass slides, air-dried, stained with May-Grünwald Giemsa dye, and read by microscope (Leitz Laborlux Microscope, $\times 50$ focus). The number of inflammatory cells (neutrophils, eosinophils) was considered as the total number of each cell type per microscope field; the data are expressed as a mean of 10 fields (9).

Immunocytochemistry

A sensitive immunoenzymatic alkaline phosphatase-monoclonal antialkaline phosphatase (APAAP) complex procedure was employed (16). Specimens were air-dried at room temperature for 30 min and submitted to 1:50 dilution of purified ICAM-1/CD54 mAb (1 mg/ml, 84H10, IgG1 – Immunotech, Marseille, France) or to 1:100 dilution of anticytokeratin mAb (CK19, IgG1, DAKO, Milan, Italy) as a marker of epithelial cells. After washing in phosphate-buffered saline (PBS), pH 7.6, samples were incubated with

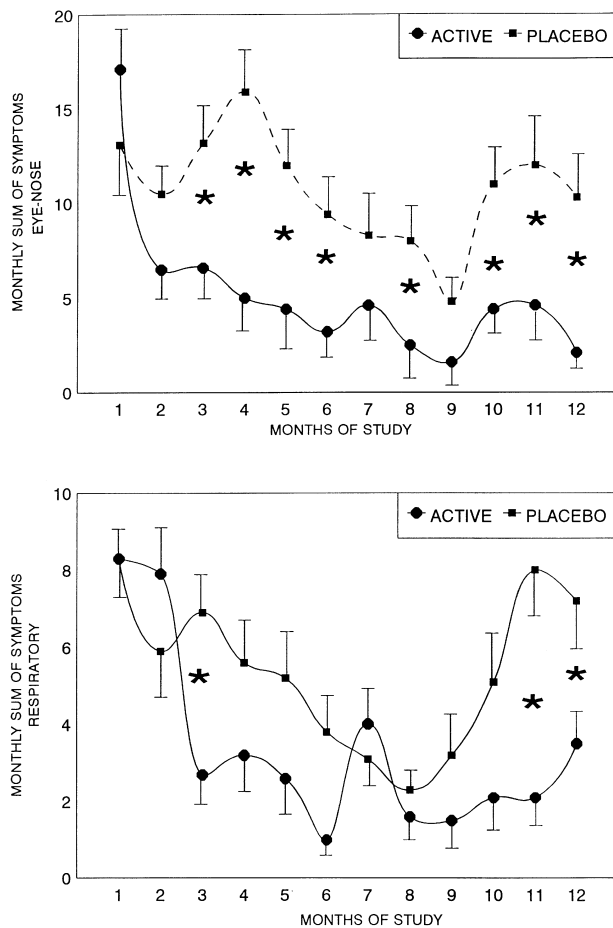


Figure 1. Rhinitis-conjunctivitis symptoms score sum (upper panel) and respiratory symptoms score sum (lower panel) month-by-month (mean $\pm$ SEM). Significant differences between two groups ($P < 0.05$) are marked by asterisk.

rabbit antimouse Ig, followed by APAAP complex. Afterward, specimens were incubated in substrate solution containing basic new fuchsin, naphthol (as biphosphate), and levamisole (as an inhibitor of endogenous alkaline phosphatase) (Sigma, St Louis, MO, USA). In control samples, either mAb or antimouse Ig was omitted. As negative isotype-control for staining on epithelial cells, an anti-T-cell (CD3) mAb OKT3, IgG1, (Ortho Diagnostic, Raritan, NJ, USA) at 1:20 dilution of the stock solution (provided by the manufacturer) was used. All preparations were counterstained with Carazzi's hematoxylin; epithelial cells were identified morphologically.

ICAM-1/CD54 expression on epithelial cells was scored according to our previous reports by a five-point rating scale, from 0 to 4 where 0=no positive cells, 1=mild positivity on 25% of epithelial cells, 2=mild positivity on 75% of epithelial cells, 3=intense positivity on 75% of epithelial cells, and 4=very intense positivity on all epithelial cells (3, 4, 15).

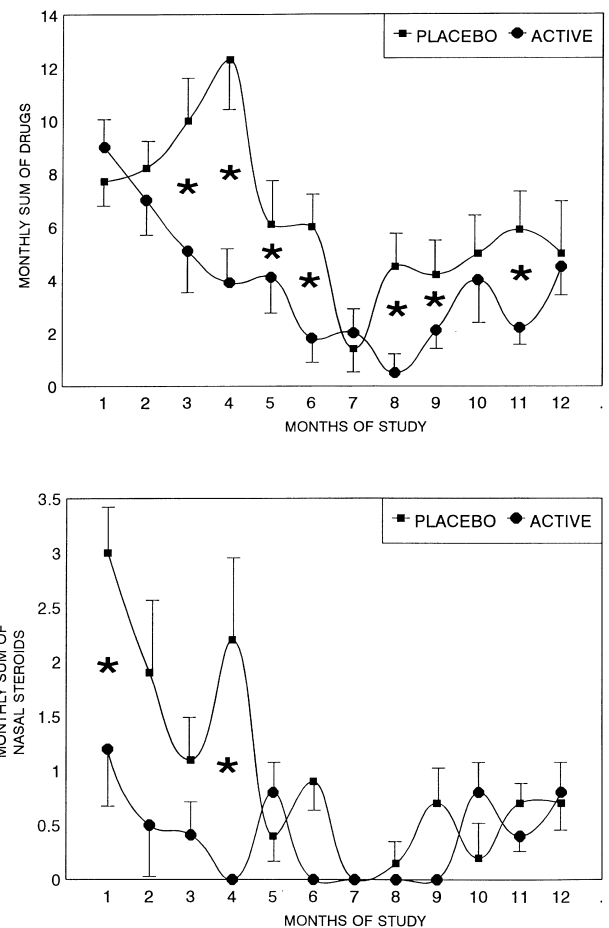


Figure 2. Allowed drug intake score sum (upper panel) and intranasal steroids intake score sum (lower panel) month-by-month (mean $\pm$ SEM). Significant differences between two groups ($P < 0.05$) are marked by asterisk.

Systemic immunologic parameters

The serum concentrations of some allergic inflammation-related mediators (soluble ECP, and soluble ICAM-1) were assessed at the four programmed control visits.

Soluble ICAM-1 was assayed by a solid-phase ELISA method (ICAM-1 test kit; T Cell Diagnostic, Inc., Cambridge, MA, USA) employing microtiter plates coated with anti-ICAM1 antibodies. The serum samples were diluted 1/100.

The samples were incubated with horseradish peroxidase-conjugated murine monoclonal antibody to human ICAM-1 for 2 h and then washed away. A chromogenic substrate was then added, and the absorbance was read after 30 min at 492 nm. Results are expressed in ng/ml according to a reference curve.

Soluble ECP was detected by double antibody radioimmunoassay (ECP RIA; Kabi Pharmacia Diagnostics AB, Uppsala, Sweden).

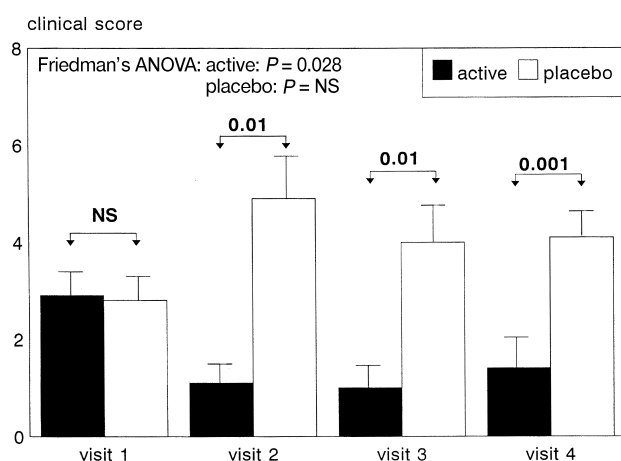


Figure 3. Clinical score of summed rhinoconjunctivitis plus respiratory symptoms (mean $\pm$ SEM) assessed by allergist at four programmed clinical visits. Intergroup comparisons are reported on bars.

A 50-ml aliquot of ^{125}I -labeled ECP and an equal amount of rabbit anti-ECP were added to serum samples and nasal lavage samples and then incubated for 3 h at room temperature. The decanting suspension (antirabbit IgG) was added, the tubes were centrifuged (10 min, 1500 g), and the pellet was then transferred on absorbent paper.

The radioactivity was measured with a gamma counter, and the results were expressed in $\mu\text{g/l}$ following a six-point standard curve.

Extra visits

The patients' parents were instructed to apply to our center for an extra visit in the case of one or more of the following symptoms: sore throat, sneezing, nasal mucopurulent discharge, headache with or without fever, and asthma exacerbation). The number of extra visits was itself considered an index of well-being.

At each extra visit, a nasal scraping for assessing the inflammatory cell count and ICAM-1 expression on epithelial cells was performed.

Safety parameters

Common safety evaluation parameters (red blood cell, leukocytes, platelets, Na, K, glucose, BUN, creatinine, ESR, and CRP) were evaluated at each control visit. An ECG was recorded at the beginning and at the end of the study to evaluate possible disturbances of cardiac rhythm.

Statistical analysis

All demographic data, including allergen content in house dust, were considered normally distributed and therefore analyzed by Student's *t*-test. Because the clinical and cytologic parameters might have been nonnormally distributed, the Mann-Whitney test was used for the intergroup comparison. Friedman's ANOVA was used for multiple nonparametric comparison within groups. *P* values less than 0.5 were considered significant.

Results

All the patients enrolled completed the study. The compliance with the treatment was satisfactory: no significant difference in the number of omitted doses during the study period was found between the active and the placebo groups (active: 16 ± 5 ; placebo 17 ± 3 ; $P = \text{NS}$).

The patients of the two groups were homogeneous at baseline, as far as the demographic data were concerned. Furthermore, the allergenic in-house exposure (Der p 1, Der f 1, and Fel d 1 levels) was comparable for the two groups, both at the beginning and the end of the study. The demographic data of the patients at enrollment are summarized in Table 2.

Clinical parameters

The monthly sum of the clinical scores for rhinoconjunctivitis are reported in Fig. 1 (upper panel). A significant difference between the two groups was evidenced in 8 out of 12 months of study (Mann-Whitney test). On the other hand, as far as the respiratory symptoms are concerned (cough and dyspnea), the symptom scores were generally low, and a significant difference between the two groups was observed in 3 out of 12 months (Fig. 1, lower panel). A significantly lower total drug intake score was observed in the actively treated group in 7 out of 12 months (Fig. 2, upper panel) than in the placebo group. The consumption of intranasal steroids was very low in both groups, as reported in Fig. 2 (lower panel). It is noteworthy that only two patients of the placebo group and one of the active group needed a short course of systemic steroid during the trial.

This result is confirmed by the analysis of the clinical scores assessed by the allergist at the four programmed visits. At the first visit (enrollment), no difference was detected between the two groups, confirming the baseline homogeneity of the patients. On the other hand, at the

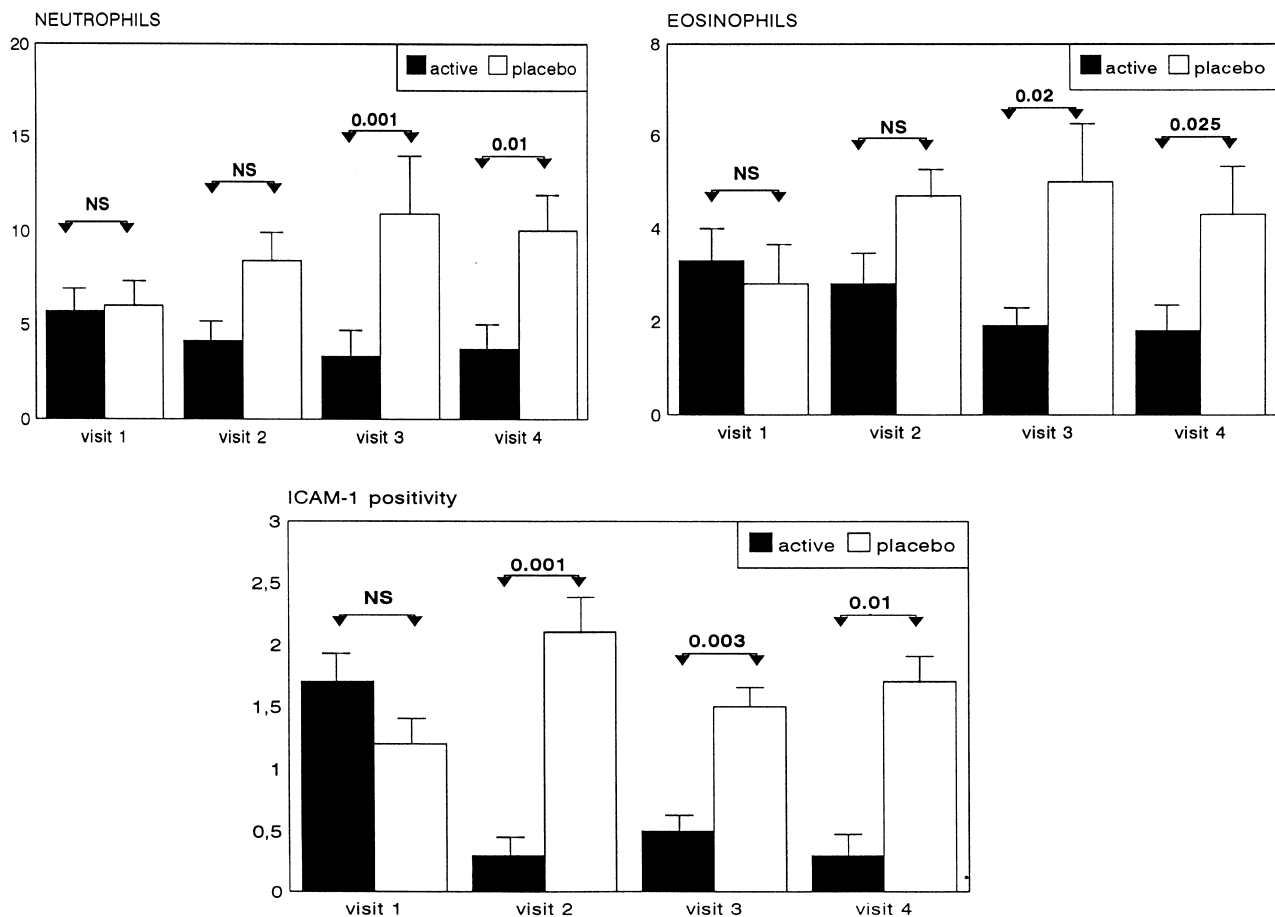


Figure 4. Neutrophils, eosinophils, and ICAM-1 positivity in nasal scrapings at four programmed clinical visits. Intergroup comparisons are reported on bars.

subsequent visits (after 4, 8, and 12 months of treatment), significant improvement was observed only in the actively treated patients, as shown in Fig. 3. This trend was also confirmed by Friedman's ANOVA.

Concerning the days of school absence due to concomitant illness, the actively treated group had a significantly lower number of school absences than the placebo group (6.9 ± 5.5 days vs 13 ± 6.5 days; $P=0.04$); in parallel, the actively treated group underwent a significantly lower number of extra visits during the study period (2.4 ± 1.5 vs 5.5 ± 1.2 ; $P=0.003$). No significant difference between the two groups was observed in the number of days of hospital admission due to concurrent disease (0.9 ± 0.6 days vs 1.5 ± 0.6 days; $P=NS$).

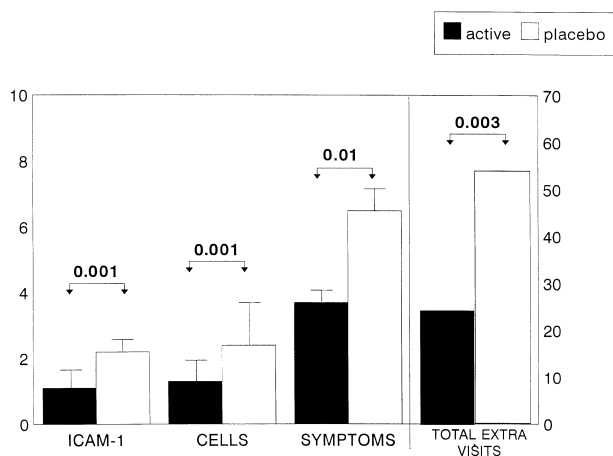


Figure 5. ICAM-1 positivity, rhinocytogram, and symptom score at extra visits, and number of extra visits. Intergroup comparisons are reported on bars.

Allergic inflammation parameters

The neutrophil count in nasal scraping was similar in the two groups at baseline and after 4 months of treatment, whereas a significantly lower count was observed in the active group after 8 and 12 months of treatment ($P=0.001$ and $P=0.01$). Similar results were obtained for the eosinophil count both at baseline and after 4 months of treatment; a significant difference between the two groups was observed at 8 and 12 months ($P=0.02$ and $P=0.025$, respectively).

Finally, the actively treated group showed a significantly lower ICAM-1 expression on epithelial cells than the placebo group from month 4 of therapy ($P < 0.01$). These results are summarized in Fig. 4.

Serum mediators

No significant difference was observed between the two groups in the ICAM-1 levels in serum assessed at the four control visits. As far as soluble ECP is concerned, a significant difference between the two groups was observed only at the end of the study (active vs placebo: 12.8 ± 6.3 vs 7.4 ± 5.5 ; $P = 0.05$).

Extra visits

The patients from the placebo group generally had a higher number of extra visits. In fact, 54 extra visits were recorded in the placebo group, and only 25 in the active one ($P = 0.003$). The evaluation of symptoms, inflammatory cell count, and ICAM-1 expression during respiratory symptom exacerbation revealed that the active group showed significant lower values of these parameters than the placebo group: 0.001 for ICAM-1, 0.001 for cell count, and 0.01 for symptoms (Fig. 5).

Safety evaluation

No side-effect that could have been related to the investigational drug (sedation, xerostomia, or constipation) was observed or reported during the whole study period nor any abnormality of the studied safety parameters. No rhythm disturbance (such as QTc prolongation) was observed in either group.

Discussion

The nose and the eye represent an almost ideal experimental model for investigating the allergic inflammatory phenomena and their modulation, since they are target organs of the allergic reaction and they are easy to study. By means of these models, we have demonstrated the involvement of the cell adhesion molecule system (ICAM-1, in particular) in the pathophysiology of the allergic inflammation, and that a minimal persistent inflammation is present in mite-allergic patients also in the absence of symptoms. In addition, the nasal and conjunctival models allowed us to demonstrate *in vivo* some of the so-called "antiallergic" actions of several

new antihistamines. These actions, which were also observed *in vitro*, are represented by the capacity of downregulating different phenomena of the allergic inflammation, such as cellular activation, recruitment, and mediator release (14). The second-generation antihistamine terfenadine was shown to be able to reduce the cellular infiltration and the expression of the ICAM-1 molecule on epithelia.

These effects of antihistamines could suggest a different therapeutic approach to the treatment of respiratory allergy, involving a continuous administration rather than an on-demand one, in order to control not only symptoms but also the allergic inflammation. Furthermore, some studies have shown that continuous and prolonged antihistamine treatment in allergic children may also have a prophylactic action and prevent the onset of asthma (12, 13, 15). Finally, antihistamines used for allergic rhinitis could also improve the lower respiratory symptoms (16).

On the basis of these premises and our clinical observations, we aimed to demonstrate formally that continuous and prolonged antihistamine treatment could not only improve symptoms but also prevent the occurrence of respiratory illness in children. In a double-blind, placebo-controlled fashion, we studied the effects of terfenadine in mite-allergic children, by evaluating both the allergic inflammation in the nose and the clinical parameters. We observed that the actively treated group had better control of symptoms, used fewer drugs, and showed a reduction of cellular infiltration and ICAM-1 expression. These facts confirm the previous observations. It is noteworthy that the children receiving the active treatment needed fewer extra visits for acute respiratory symptoms and had fewer school absences. At the nasal scraping made at each extra visit, these children showed a better control of the allergic inflammation with respect of the actively treated group. Although terfenadine has been withdrawn for safety reasons in Italy since the end of 1996, no side-effect was observed in our study.

An intriguing hypothesis to explain the observed effects of terfenadine could be its effect on ICAM-1. In fact, the minimal persistent inflammation (with a constant weak expression of ICAM-1 on epithelia) may be responsible for the enhanced susceptibility of allergic children to rhinoviral infections (17, 18), especially since ICAM-1 is the main receptor for human rhinoviruses (9). The downregulation of ICAM-1 by terfenadine could be responsible for the observed effects, in addition to the fact that good control of rhinitis is known to improve asthma symptoms also. Obviously, the

clinical observations herein reported need formal scientific evidence such as the identification of viruses in the upper respiratory tract of patients, but they may suggest a possible new therapeutic approach.

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